



Oxford Vaccine Group
University of Oxford
Centre for Clinical Vaccinology and Tropical Medicine,
Churchill Hospital, Headington, Oxford OX3 7LE
Tel/Fax: 01865 611400/289695 info@ovg.ox.ac.uk www.ovg.ox.ac.uk



OXFORD VACCINE GROUP

Investigating Typhoid Fever Pathogenesis (TYGER)

Study Information Booklet

You are invited to take part in a study to investigate the human response to typhoid infection. 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 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 taking the time to consider taking part in the study.

Contact Details

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital
Oxford OX3 7LE
Tel/Fax: 01865 611400/289695
Email: info@ovg.ox.ac.uk
Website: www.ovg.ox.ac.uk

Who are the Oxford Vaccine Group?

The Oxford Vaccine Group (OVG), 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 7,000 participants in the Thames Valley area have taken part in our research studies.

What is typhoid fever?

Typhoid fever is an infection caused by the bacteria *Salmonella* Typhi. Although it is from the same family as the *Salmonella* bacteria that cause gastroenteritis (vomiting and diarrhoea) in the UK, it is quite different. *Salmonella* Typhi is very rarely found in the UK and mainly causes infection in developing countries. It is thought to cause illness in approximately 22 million people every year and up to 200,000 deaths, mostly in children. People from the UK could be exposed to the infection if travelling to these countries. Typhoid infection is most common in poor communities with poor sanitation and water supplies. The bacteria are spread when infected individuals' faeces contaminate food and water sources. Symptoms of infection include headache, fever and general aches and pains. If not treated properly typhoid infection can lead to severe complications and even death.

Are there vaccines against typhoid?

Yes, oral and injectable vaccines are currently used to prevent infection with *Salmonella* Typhi (typhoid fever). However, these vaccines are 30-60% effective at preventing typhoid infection and currently no typhoid vaccine is licensed for use in young children. More research is needed to better understand typhoid so that we can develop better typhoid vaccines.

What is the purpose of this study?

In this study we aim to understand more about the *Salmonella* Typhi bacteria and how it causes illness. Specifically we want to understand the importance of a toxin produced by the typhoid bacteria, called the **Typhoid Toxin**. Our goals are to better understand typhoid fever, develop new diagnostic tests and contribute to development of new vaccines against *Salmonella* Typhi.

What is the Typhoid Toxin and why are we studying it?

During an infection, some bacteria produce toxins that are responsible for causing disease. Examples of this include the bacteria that cause tetanus, diphtheria and whooping cough. The toxins produced by these bacteria are crucial to causing disease and if we can protect people against the effect of these toxins through vaccination, we may be able to protect people against these diseases.

The **typhoid toxin** has only recently been discovered. It is made only by the typhoid bacteria and closely related bacteria, such as paratyphoid. Earlier studies in the lab have shown that the typhoid toxin is likely to be very important in causing typhoid fever and may explain some of the symptoms seen during illness. It is thought that the typhoid toxin could explain why the typhoid bacteria behaves differently to other members of the *Salmonella* family and may even explain why the typhoid bacteria only infects humans and not other animals.

The exact role of the **typhoid toxin** during infection in humans has never been studied before, partly because it has only recently been discovered. Studying this might impact on how we design new vaccines against typhoid, because if the typhoid toxin is important in causing symptoms of typhoid, then future vaccines could be designed to try to block the action of this toxin.

What does the study involve?

We aim to enrol approximately **40** participants into this study.

We will be undertaking a 'challenge' with two strains of the typhoid bacteria (*Salmonella* Typhi). Participants will be exposed to live *Salmonella* Typhi under tightly controlled circumstances, by asking them to swallow a drink that contains the bacteria. After the challenge we will closely monitor participants for a period of two weeks, treating participants with antibiotics as soon as they show any symptoms of infection. This process has been undertaken by participants in previous Oxford Vaccine Group studies since 2011.

We will use two strains of the typhoid bacteria. Half of the participants (20) in this study will be challenged with a 'normal' strain of the typhoid bacteria, called **wild-type strain**, which has been used in earlier challenge studies. The other half of the participants (20) will be challenged with a modified' strain of the typhoid bacteria that is not able to produce the typhoid toxin, called the **toxin-negative strain**. Previous studies show that by giving a specific dose of the **wild-type strain** of *Salmonella* Typhi, 60% to 70% of people exposed to the bacteria will develop typhoid infection. If fewer people are infected with typhoid after receiving the **toxin-negative strain** (less than 60%), then this suggests that typhoid-toxin, specifically, is important in causing typhoid disease

The toxin negative strain is a genetically modified organism (GMO) that has been engineered not to produce the typhoid toxin. This means that the two strains are identical, except that wild-type strain can produce the typhoid toxin and the toxin-negative strain cannot. By comparing the response to challenge with both strains, we hope to understand the importance of typhoid toxin in causing typhoid infection.

In addition, we will be able to study how the immune system responds to the different strains of typhoid and how this might help to prevent typhoid disease. This will add to our general understanding of typhoid and vaccine development.

Will I know which strain I will be challenged with?

Participants would be randomly separated into two groups to be challenged with either the **wild-type strain** OR the **toxin-negative strain**. This means a computer programme would randomly assign participants to receive either challenge strain. This is similar to a coin-toss, meaning that you have a 50:50 chance of being assigned to receive one or the other challenge strain. The study team would not be able to influence which challenge strain you are assigned and would not know which challenge strain you had received during the study. We would only tell you which strain you were challenged with at the end of the study.

Who can take part in the study?

We are looking to recruit volunteers who are healthy and between 18 to 60 years of age.

- If you had any significant medical conditions (including significant psychiatric illness requiring hospitalisation), a history of alcohol or drug abuse, are pregnant or planning on becoming pregnant, or are breastfeeding you may not be able to participate.
- If you lived in a country where there is typhoid disease for more than 6 months, then you may not be eligible to participate. Typhoid is prevalent in the following regions: South Asia (e.g. India, Pakistan), Southeast Asia (e.g. Vietnam, Thailand) and certain areas of Africa and Central/South America.
- In particular we are looking to recruit volunteers who have not received a typhoid vaccine injection within the past 5 years. Typhoid vaccines are not part of the routine vaccination schedule in the UK, but are

frequently given to people who are travelling to countries where they may be exposed to typhoid. If you have received a typhoid vaccine injection more than 5 years ago, you may still be eligible to take part in the study, depending on the result of a blood test taken at the screening visit (please check with your GP if you are uncertain of your vaccination history or contact the study team if this requires further clarification).

- If you live or work with vulnerable people (e.g. people with poor immune systems and young children) or work in professional food handling then you may also be excluded.
- You could not take part if you have an allergy to the antibiotics used in this study (e.g. ciprofloxacin, azithromycin - described below).

If you are unsure whether or not you will be eligible for the study, you can speak to a member of our team using the contact details at the end of this information booklet.

You would need to be available for a month following the challenge, where you would attend **daily visits for at least 2 weeks** and would need to complete a **2 week course of antibiotics**. 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 on a daily basis). Follow up would then be at 1, 3, 6 and 12 months after the 'challenge' day.

Participants would need to attend visits at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at the Churchill Hospital site in Oxford.

What happens in this study?

Participants will be given a specific amount of live *Salmonella* Typhi bacteria to drink. The doctors and nurses at the Oxford Vaccine Group will then monitor participants daily in the clinic for the next two weeks to find out what symptoms they develop. Blood and stool (faeces) samples will be taken to find out how participants respond to the bacteria. We do not expect everyone to develop typhoid infection and some participants may not feel unwell at all. We don't know if the response to challenge with the wild-type or toxin-negative strains will be the same or different. Regardless of this, everyone will receive antibiotics either when they develop typhoid infection or 14 days after they have drunk *Salmonella* Typhi if they do not develop infection.

What are the risks of undergoing challenge?

The risks of taking part in this study are very low provided that you return for follow-up as outlined in this booklet. If untreated, typhoid infection can result in serious illness or even death. However, nearly 2,000 people have been challenged with typhoid bacteria during studies in the United States in the 1960s and at the Oxford Vaccine Group since 2011 and all have made a complete recovery.

Typhoid Infection

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

- fever
- headache
- feeling tired and generally unwell
- muscle or joint ache
- abdominal discomfort
- loss of appetite

In some circumstances, it is recommended that you take time off work/study if you develop symptoms of typhoid infection.

Severe problems are unlikely as we would treat participants very early on in the course of illness (within 12 hours of onset of fever or if a participant has bacteria in their blood). Severe complications are rare and mainly occur when typhoid fever is not treated properly or immediately. If typhoid fever is left untreated, possible complications include bleeding from the gut, a hole developing in the gut, becoming a carrier of typhoid, 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.

It is possible that typhoid (as well as the antibiotics used to treat the infection) can have a transient effect on your gut and the number, variety and types of bacteria that naturally live in your body. Whilst we expect this to be a short term effect, we will be collecting samples up to one year after challenge to study the impact of challenge on the gut environment.

Carriage

A small percentage of people who contract typhoid infection in the field can go on to carry the bacteria and excrete the bacteria in their stools. These people are known as 'carriers' and we know that this almost always happens in people with gallstones. For this reason we would do an ultrasound scan of your gallbladder prior to challenge and if we found that you had evidence of gallstones, you would not be able to take part in the study. In the unlikely event that you did become a carrier you would be referred to an infectious diseases specialist for further antibiotic treatment.

We also collect 3 stool samples after you have completed your antibiotics to prove that the typhoid bacteria have been fully cleared. Very rarely, stool cultures can remain positive even after you have completed a course of antibiotics. As above, in the unlikely event that this were to occur, you would be referred to an infectious diseases specialist for further antibiotic treatment.

General risks

This study involves several blood tests. 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.

Can I give typhoid infection to anyone else?

Typhoid infection 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 cases occur within a household and other close contact situations but transmission is extremely unlikely if good hygiene practices are followed.

We would give you detailed advice on how to make sure you don't give typhoid infection to other people and also provide you with antibacterial soap and disposable towels to help. It is very unlikely that anyone could contract typhoid 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. 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.

Study Procedures

Recruitment

If you expressed an interest in taking part, a member of the Oxford Vaccine Group would contact you by telephone to discuss the study and answer any questions you may have. Following this, if you are interested and seem suitable for the study we would arrange for you to come to our clinic for a screening visit.

Screening Visit

The purpose of screening is to assess whether you are able to participate in the study.

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 is involved. You would be allowed as much time as you feel necessary before making any decision on whether or not to take part.

If you wish to proceed, we would ask you to sign an **informed consent form** and complete a short quiz to ensure you have understood the study. 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 blood sample to ensure you are healthy. Blood will be screened for typhoid antibodies, 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). 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 a **gallbladder ultrasound** to check for gallstones, which can cause you to carry *Salmonella* Typhi. For all females, we would perform a pregnancy test on your urine sample. We would also collect a sample of saliva and a nasal swab. After the screening visit, we would contact your GP to confirm your eligibility.

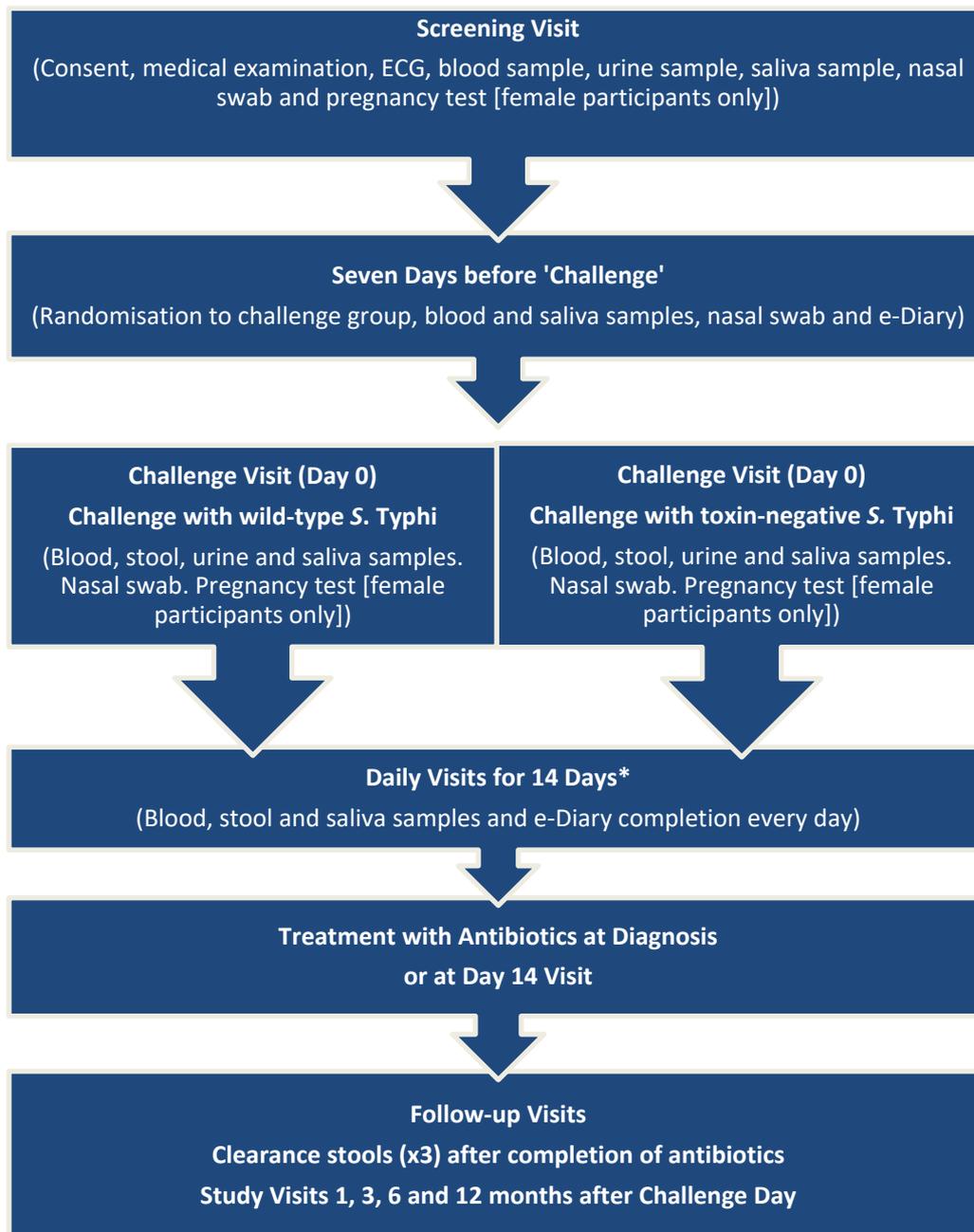
During your screening you would be asked to provide your National Insurance number (or passport number if you do not have a National Insurance number). This would be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. The Trial Over-volunteering Prevention Service (TOPS) database is to ensure safety of all our participants in this study and therefore if you are unwilling to have your information submitted on TOPS you would not be able to take part in our study. More information can be found at <http://www.hra.nhs.uk/about-the-hra/our-committees/the-over-volunteering-prevention-system/>.

Once the study team have confirmed your suitability for the study, we would inform you and arrange a date for your first visit. 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 make a decision there and then.

Overview of study visits



*Additional safety visits may be required at the discretion of the study team.

Pre-challenge visit (7 days before challenge)

You would be given a date and time to come to 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 since we last saw you.

We collect blood and saliva samples from you and take a nasal swab. We would get you set up with an electronic diary card (e-diary) that you fill in for 21 days, recording your temperature and any symptoms you may have.

At this visit, we would randomly allocate you to a challenge group with one of the two *Salmonella* Typhi strains. We would then confirm the date and time for your challenge visit one week later.

Challenge day (Day 0) – Start of the intensive monitoring period

The challenge day involves having **two** appointments at the CCVTM, Churchill Hospital. You would be asked to come to the clinic first thing in the morning with 2 fresh stool samples. We would check that you are happy to remain in the study and ask if there have been any changes since we last saw you. You would have a blood test taken and women would have a urine pregnancy test performed. You would be asked to fast for 90 minutes before the visit.

We would give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella* Typhi) followed by a drink containing one of the two *Salmonella* Typhi strains. You would then be asked to fast for a further 90 minutes.

We would then see you at approximately 12 hours after the challenge to collect an additional blood sample. We would check that you still had access to your e-diary and your thermometer. We would ask you to record your symptoms and your temperature in the e-diary twice a day for the following three weeks. During this time 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 typhoid infection.

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 will be acceptable to continue to take long term medications – one of the study doctors will discuss this with you during screening. Of course, 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, some antibiotics could affect the *Salmonella* Typhi 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 happens at the follow-up visits?

Follow up visits during the challenge period would take place at the CCVTM. At the visit we would review your symptoms as recorded in your e-diary, measure your temperature, pulse and blood pressure and take a blood sample. These samples would be examined for the typhoid bacteria and also to study your body's immune response to typhoid infection. Blood tests will also be taken for genetic analysis to see whether a particular genetic makeup can protect against typhoid infection and affect your response to the challenge. For this reason it is necessary for us to record your ethnicity as this influences how we interpret your genetic tests.

It is essential that you are available to attend for the study visits, 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.

After challenge you may develop symptoms of typhoid infection or remain well. Some people are diagnosed with typhoid infection without having any symptoms. For 2 weeks after challenge we would need to see you every day for approximately 30 minutes and would also contact you in the evening by text or telephone call. We would ask you to bring 2 fresh stool samples to each visit.

What happens if I get typhoid infection?

The main symptom of typhoid infection is fever (a high 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 your temperature was high for 12 hours or if we found bacteria in your blood then you would be diagnosed with typhoid infection. You would then be treated with a course of antibiotics to clear the typhoid infection.

Once you had started the course of antibiotics, paracetamol could be taken to lower your temperature, which we will provide. If you develop typhoid infection, you could feel unwell for several days. With early antibiotic treatment people usually do not develop severe symptoms. If you unexpectedly became severely unwell during this time then you might be admitted to a hospital ward as a precaution until you had recovered, but it is very unlikely that this would be necessary.

For safety reasons, we would need to see you when you are first diagnosed and then 12, 24, 48, 72 and at least 96 hours later. This is to ensure that you are responding well to the antibiotic treatment. Depending on when/if you are diagnosed, this may require some additional visits to the clinic.

What happens if I do not get typhoid infection?

If you had not been diagnosed as having typhoid infection, at day 14 we would give you a course of antibiotics. This is to ensure elimination of any *Salmonella* Typhi 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 one of the best treatments for typhoid infection and is widely used for treatment of many different types of 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 it can cause rash, heart rhythm abnormalities, mood disturbance, 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, including azithromycin, trimethoprim/sulfamethoxazole or amoxicillin.

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 the e-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 its benefits and side effects, will be discussed with you beforehand.

What samples will you collect?

We would take blood and urine samples as part of the screening visit, to help us assess your general health. Blood and stool 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. At some visits we will also collect a urine sample. 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.

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 typhoid infection or not. A maximum of 1060ml of blood will be taken over the course of the study. As a comparison, if you were to give blood to the National Transfusion Service a woman would be able to give a maximum of 1,410ml per year, and men 1,880ml per year. For this reason, participants will be asked not to donate any blood while participating in the study.

We are interested in studying how the bacteria that naturally live in your gut and other parts of your body affects challenge with the typhoid bacteria and vice-versa. In order to study this, we will collect samples of stool and saliva as well as swabs from the nose at certain points during the study.

What would happen to any samples I give?

The blood, saliva and stool samples as well as the nasal swabs collected during this study would be analysed in the Oxford University Hospital and University of Oxford research laboratories. We would also send some samples to other researchers working with us on this research project, including researchers outside the European Union. These samples would be anonymised.

What else do I need to know?

You would be required **to provide a name and a 24 hour phone number** for someone who lives with, or near you, who would know where you are for the duration of the study, and who is 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. going to your home). If study staff still could not locate you, they might need to inform the police to ensure your safety.

If you chose to take part in this study, we will be asking for your separate permission to store blood (including DNA), saliva, stool and nasal swab samples, 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 typhoid study, and you are free to say no to this and continue to take part in this typhoid study if you wish.

What if any of my test results were abnormal?

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 (we would not report them to anyone else without your permission). For example, a new diagnosis of high blood pressure might be made. Any newly diagnosed conditions would be looked after by your GP.

Pregnancy

Typhoid infection can potentially be dangerous during pregnancy both to the mother and to the unborn child. Women would therefore be asked to use an effective method of contraception until tests show that the *Salmonella* Typhi bacteria had been fully treated. A pregnancy test would be carried out at the screening visit, before challenge and prior to starting antibiotics.

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

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 has a problem with their immune system until we were absolutely sure that you did not have the *Salmonella* Typhi bacteria in your body (at least six weeks after challenge).

Food handlers

Salmonella Typhi can be transmitted in food handled by people who are infected with *Salmonella* Typhi. If your work involves handling 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 typhoid infection (including those under 2 years of age) or in whom typhoid infection would have particularly serious consequences then you would not be allowed to return to work until 3 consecutive negative stool samples have been obtained at least 48 hours apart, commencing one week after completion of treatment.

Reimbursement

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

- Travel expenses: £15 per visit (total for 28 visits = £420)
- Inconvenience of blood tests: £10 per blood donation (total for 27 blood tests = £270)
- Time required for visit: £20 per visit (total for 28 visits = £560)
- Time off work compensation: £150 per day for 10 days (total = £1500).

Participants will receive a maximum of £2,750 if they remain in the study for the entire period and attend all study visits. Payments will be made via internet bank transfer. Participants will be asked to provide banking details including account name, sort code and account number. All details will be stored confidentially and retained by the Oxford Vaccine Group while the participant is actively involved in the study.

Participant payments will be requested after you have attended the following visits: Ultrasound, Day 14, Day 90, Day 180, and Day 365. Payments usually take 4-6 weeks to be processed.

Note that “time off work” reimbursement is limited to the 10 days after challenge. If you were to take time off work after this period we would not be able to reimburse you for this.

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 typhoid infection we may ask your permission to take a photograph/film. Medical photography/film can be useful in clinical discussions, scientific publications and educational events such as conferences. 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. 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.

What is expected of me during the study?

- You must stay in close contact with the study team until you have completed antibiotics.
- 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.
- You must provide all household and close contacts with study information given to you by the study team which will offer them screening for *Salmonella* Typhi infection.
- You need to attend all study visits.
- You should record in the study e-diary all of your symptoms and your temperature for 21 days (from 7 days before challenge to 3 weeks after challenge).
- After *Salmonella* Typhi 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.
- Female participants should use an effective method of contraception until they are cleared of *Salmonella* Typhi bacteria, including barrier contraception whilst taking antibiotics.
- You must provide 3 stool samples after the completion of antibiotics so we can ensure you are clear of typhoid.

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.

If you change your mind and withdraw during the study, 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.

Whatever you choose it's 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.

What happens if I don't 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 without giving a reason. If you wish to leave after drinking the *Salmonella* Typhi bacteria then you would need to take the course of antibiotics and provide stool samples after this, as very serious consequences can occur in individuals with untreated typhoid infection. We would also need to ensure that you had been treated appropriately and so would refer you for follow up with either your own GP or Public Health England. This follow up would include you providing stool samples, ensuring you are clear of typhoid.

Is there someone I can contact during the study?

You would have access to a study doctor 24 hours a day until the end of the study. It would be very important that you stay in close contact with the study team and let us know as soon as you get a temperature or feel unwell in any way.

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. We hope that the knowledge gained from this study will contribute to the understanding of typhoid disease, which could lead the development of improved vaccines against *Salmonella* Typhi.

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. 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 Public Health England and your own GP – see below). Your information would be stored on a secure server, and paper notes would be held by the Oxford Vaccine Group in a locked cabinet. Once the study has been 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 trial 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.

Anonymised data and samples would be sent to other researchers working with us on this research project, including researchers outside the European Union and the study funders.

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 prevent you from taking part in this study. 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. 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 and those that developed typhoid infection and/or have *Salmonella* Typhi bacteria found in their stools. This is to ensure that there is independent oversight of the public health aspects of this trial. 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.

What will happen at the end of the research study?

The results of the research will be published in a scientific medical journal, which 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?

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

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. 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 Professor Andrew Pollard, Director of the Oxford Vaccine Group, (Tel: 01865 611400, Email: 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 organising and funding the study?

The study is funded by [Funder details].

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 (16/SC/0358) and has also been approved by the NHS (Research & Development approval).

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

- We would ring you to check that it is appropriate to include you in the research.
- You would then attend a screening visit at the CCVTM where you would have a blood test, urine test, nasal swab and saliva sample taken (and a pregnancy test for women). An ultrasound scan of your gallbladder would then be arranged. These are to assess your eligibility for the study.
- Following satisfactory screening results you would be enrolled into the study.
- You would be challenged with one of two variants of *Salmonella* Typhi by swallowing a drink that contains the bacteria.
- You would attend clinic appointments at least once a day for 14 days during which time blood and stool samples would be collected.

- If you get diagnosed with typhoid fever, you may need to attend for extra safety visits.
- You would be asked to fill in an e-diary twice a day for three weeks after challenge to record any symptoms you have as well as your temperature.
- You would be treated with antibiotics if you were diagnosed with typhoid infection or, if you did not get typhoid infection, 14 days after typhoid challenge.
- We would continue to see you for the occasional clinic visit up to 12 months after the start of the study.

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 <http://trials.ovg.ox.ac.uk/tyger>
- email info@ovg.ox.ac.uk

Yours sincerely,

Prof Andrew J Pollard
Professor of Paediatric
Infection & Immunity
Honorary Consultant
Paediatrician

Prof Brian Angus
Clinical Tutor in Medicine
Honorary Consultant
Physician

We do not have your personal details unless you have specifically provided us with these. If you do not wish to receive invitations of this kind in the future, please contact the NIHR CRN: Thames Valley and South Midlands - Primary Care team on; Email: optout.tvsm@nhr.ac.uk, Phone: 01865 223295

Address: Optout TVSM, NIHR Clinical Research Network: Thames Valley & South Midlands, TVCN Offices, Block-8, Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford OX3 7HE

Please provide your full name, date of birth and post code, if you do not provide this data it is difficult to ensure you are removed from future mail outs.

If you would like to change your mailing preferences on the electoral roll, you can contact the mailing preference service on; Email: mps@dma.org.uk or Tel: 02072 913310



Investigating Typhoid Fever Pathogenesis (TYGER)

Informed Consent Form

Participant's name: _____

Participant initials: _____

Screening number: SPT – 04 |__| |__| |__| |__|

Please **initial** in each box if you agree with the statement

I have read the 'Investigating Typhoid Fever Pathogenesis (TYGER)' Study Information Booklet (Version X.X, dated DD-MMM-YYYY).

I have had the opportunity to discuss the study, to ask questions about the study and I am satisfied with the answers and explanations that have been provided.

I have spoken with Dr/Nurse _____.

I understand that I am free to withdraw from the study at any time, without having to give a reason for leaving and without affecting my medical care.

I have received detailed information about the treatment schedule and its importance.

Should I wish to withdraw after I have been challenged with *Salmonella* Typhi, I understand that I must take a course of antibiotics and will be asked to attend for further visits for safety reasons and that if I fail to do so Public Health England will be informed.

I understand that should I fail to return for review or to take the full course of antibiotics I may become seriously ill and could even die.

I will bring the 24 hour contact reply slip to the first study visit, signed by my 24-hour contact. I agree that the study team may contact this person if I cannot be contacted during the study.

I agree to my GP being informed of my participation in this study including information about diagnosis, treatment and clearance samples. I agree to my GP and/or other treating doctors being approached for additional information regarding my medical and vaccination history.

I understand that Public Health England will be informed of my participation in this study including information about diagnosis, treatment and clearance samples.

I agree to inform my household and close contacts of my participation in the trial, and will give them the information letters provided by the Oxford Vaccine Group.

I agree to my National Insurance (if UK citizen) or Passport number being used to register me on TOPS. I understand that it will be stored electronically for the duration of the study.

I understand TOPS is a Health Research Authority database that aims to prevent healthy volunteers from taking part in too many studies. I understand that only staff at OVG and other research units can use the database and OVG may call other units, or OVG may be called, to check volunteer details.

I agree to provide my bank account details including my account name, sort code and account number for reimbursement purposes. I understand that my banking details will be stored electronically for the duration of my participation in the study. I agree that if a conflict is found on TOPS, OVG can share relevant information with other research groups and source relevant information from other research groups.

I agree to refrain from donating blood for the duration of the study.

I agree to OVG storing my personal information as described in the information booklet.

I agree to OVG taking and storing my blood and stool samples as described in the information booklet.

I agree to my anonymised data and biological samples being sent and stored outside of the European Union for analysis by collaborating research groups as described in the information booklet.

I understand that some of my blood will be used to investigate the genetic factors determining the response to *Salmonella* Typhi infection.

I consider these samples a gift to the University of Oxford and I understand I will not gain any direct personal benefit from this.

I understand that I should not be involved in commercial food handling until I am shown not to be infected with *Salmonella* Typhi.

I understand my occupation must not involve direct contact with young children (defined as those attending pre-school groups or nursery or aged under 2 years) or patient contact in a health care setting until I am shown not to be infected with *Salmonella* Typhi.

I understand I should not have a household contact who is immunocompromised or children under the age of 2 or older children who are attending pre-school or nursery.

I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the study team, the University of Oxford (Sponsor), regulatory authorities or the Oxford University Hospitals NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

Women only: I understand the need to ensure that I or my partner use effective contraception one month prior to challenge and continue to do so until I am shown not to be infected with *Salmonella* Typhi. I also understand the need to use barrier contraception while taking the course of antibiotics.

For those involved in the provision of health or social care to vulnerable groups only: I agree to my employer being informed of my participation in the trial

If all of the applicable sentences above are initialled, meaning “yes”, then please continue:

I voluntarily agree to take part in this study

Name:

Signature: Date: |__ __| |__ __| 20|__ __|

Investigator's/Nurses name:

Signature: Date: |__ __| |__ __| 20|__ __|

