



## Understanding typhoid disease after vaccination

### Information Booklet for Participants

We would like to invite you to take part in a study designed to help accelerate the introduction of new typhoid vaccines. This booklet contains information outlining the study and describes what would be involved if you were to take part.

To help you decide whether to take part, it is important to understand what this study is about and what your participation would involve. Please take time to read the information carefully and discuss with others if you wish. If you would like any further information please contact us here:

#### Oxford Vaccine Group

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**Thank you for your interest in our study!**



Oxford Radcliffe Hospitals   
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Health Research

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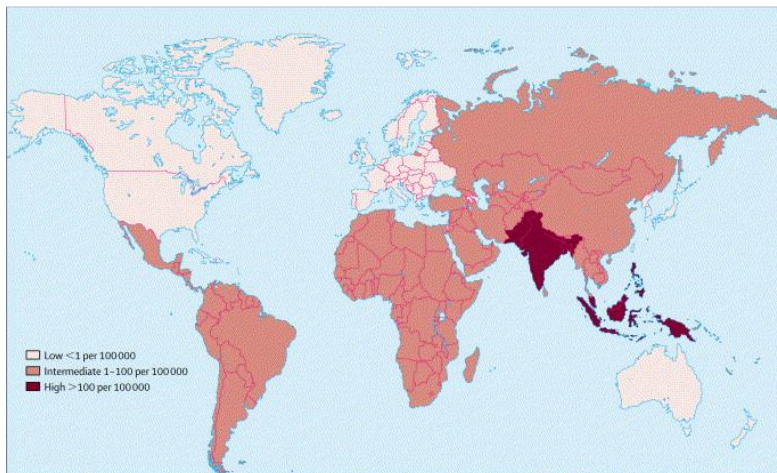


### **Who are the Oxford Vaccine Group?**

The Oxford Vaccine Group is an independent research team based at the Centre for Clinical Vaccinology and Tropical Medicine at the Churchill Hospital. We form part of the Oxford University, Department of Paediatrics and conduct research looking at new and improved vaccines for the prevention of infectious diseases in both adults and children. In the past 5 years alone, over 7000 participants in the Thames Valley area have taken part in our studies. We started our programme of research into typhoid fever, typhoid vaccines and new diagnostic tests for typhoid fever in 2010.

### **What is typhoid fever?**

Typhoid fever is a food and water borne infection caused by the bacteria *Salmonella Typhi*. Although uncommon in the UK, typhoid fever affects around 30 million people worldwide each year, of whom approximately 200,000 die. Most typhoid infections occur in resource poor settings in tropical regions (see map below), and so typhoid is also a major problem for people travelling to these areas. Trying to gauge



***A map showing the rate of enteric fever (due to typhoid and paratyphoid infection) worldwide in 2005***

the precise number of people infected is difficult, as the current tests for infection are not very good.

A week or so after infection, which generally occurs by inadvertently swallowing the *Salmonella Typhi* bacteria, typhoid causes a high temperature and general feeling of being unwell. Further symptoms may include a headache, constipation and muscle or joint pains. Unlike other types of *Salmonella*, *S. Typhi* rarely causes diarrhoea.

Early treatment at this stage is effective in preventing people becoming more unwell, however, if typhoid fever is left untreated for several weeks complications can develop. These complications can be serious or even life-threatening and are more often seen in countries where typhoid fever is common.

### **Are there not vaccines against typhoid fever already?**

We have been using vaccines to protect people against typhoid fever for almost a century, and you, or people you know may have received a typhoid vaccine before. Unfortunately the vaccines currently available are not very effective, particularly in countries where there is a lot of typhoid fever, and cannot be given to young children (below the age of 5). We desperately need new, better vaccines; recent advances in this field mean that there are now several vaccine candidates that are ready to be tried.

The development and testing of new typhoid vaccines is difficult, however, we do not understand very much about how the body responds to *Salmonella Typhi* bacterial infection and therefore which bits of the immune response are important in protecting us against the infection.

### **What is the purpose of this study?**

The purpose of this study is to investigate how effective two typhoid vaccines are in preventing volunteers developing typhoid fever. This study will provide important information about the how the immune system protects us against typhoid infection as well as showing us how effective the vaccines are in preventing infection. Other things we hope to learn from this study include:

- how individuals respond to the vaccines used, including whether there are any reactions to the vaccine,
- how vaccination alters the symptoms experienced with typhoid infection,
- how the body's immune system responds to typhoid vaccines and which features of this response may protect from future infection,
- which markers in the blood or other samples indicate early typhoid infection
- establish research methods that can be used for future new vaccines and related diseases.

Some of these findings will form part of the educational requirements for a research PhD.

### **Why have I been invited to take part?**

We are inviting up to 99 healthy adults aged between 18 and 60 years to take part in this study. Volunteers with any significant medical conditions (including depression or psychiatric problems), who have been vaccinated against typhoid fever, have a history of alcohol or drug misuse or women who are pregnant or planning to become pregnant would not be able to participate. Similarly, those in contact with individuals who may be at a higher risk of infection were they to become infected, including those caring for young children or vulnerable adults, would not be able to participate. Your participation in this study is at the researchers' discretion.

### **Do I have to take part?**

Taking part in this research study is completely voluntary. If you do decide to take part, you will be given this information booklet to keep and be asked to sign a consent form indicating that you are satisfied with the information supplied to you and that you have had sufficient opportunity to ask us questions.

### **What if I change my mind about taking part?**

You are free to change your mind about taking part in this study at any point, without needing to give us any explanation. If you do change your mind, you may be asked to return to the clinic for safety follow-up visits and you may still need to take the full antibiotic course.

### **What will taking part in this study involve?**

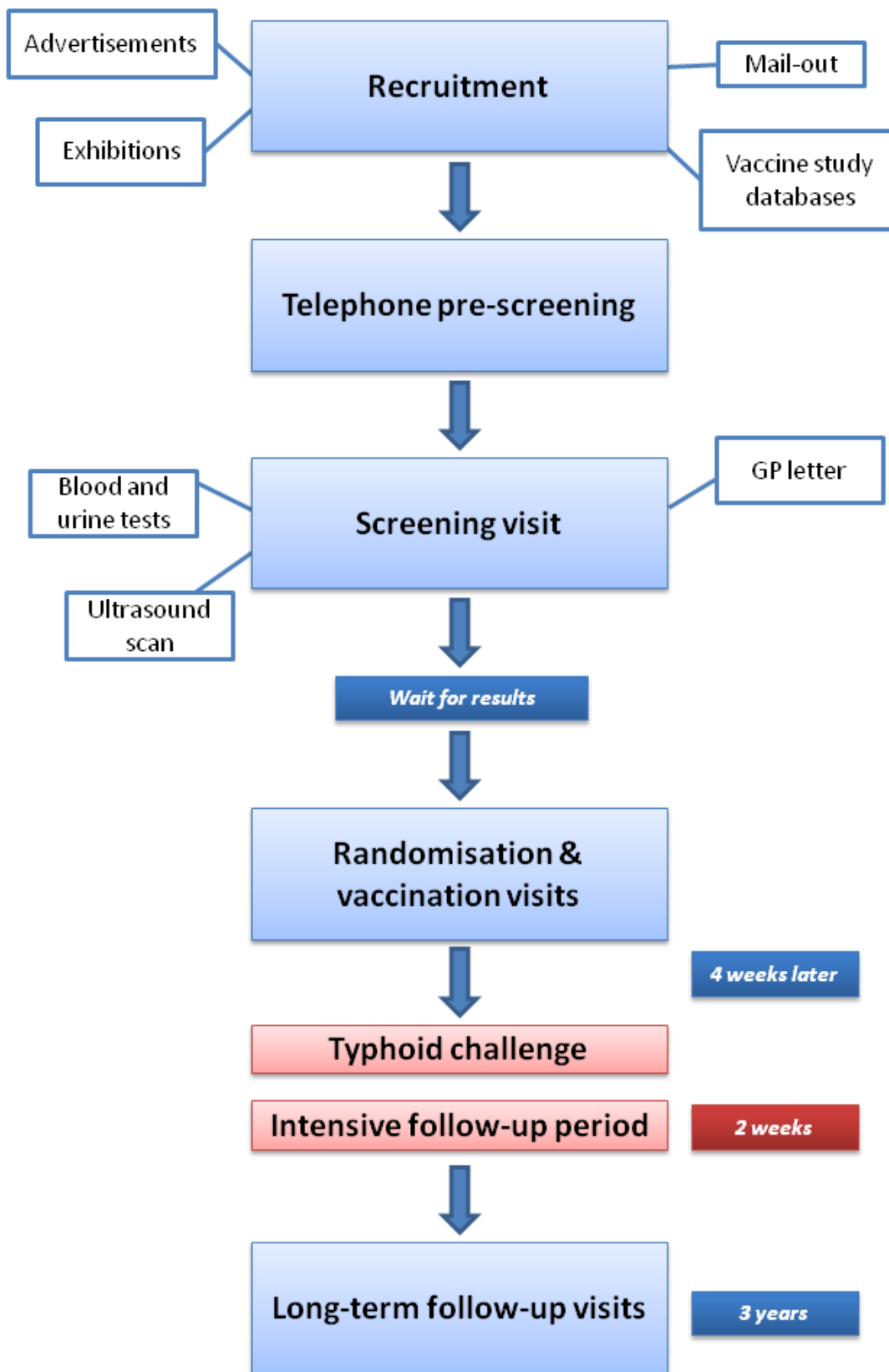
An overview of what is involved in taking part in this study is given in the flow chart below. If you choose to take part in this study, we would arrange for you to come for a 'Screening visit' in order for us to describe the study to you in detail and answer any questions that you may have to enable you to sign the consent form. If you fulfilled our inclusion/exclusion criteria we would then ask you about your medical history, perform a physical examination, take blood and urine samples and perform an ECG (heart tracing). We would also arrange for you to have an ultrasound scan of your abdomen performed to make

sure you didn't have any gall-stones and contact your GP to ask for their agreement to enrol you into our study.

After satisfactory completion of the screening procedures we would arrange for you to come in for a vaccination visit. At this visit you would receive a randomly allocated typhoid vaccine. The vaccines are described in more detail below and are anticipated to be well tolerated; however, as with any vaccine or medicine, you may experience side-effects that prevent you carrying on with everyday activities. One month later we would 'challenge' you with *Salmonella* Typhi bacteria by asking you to drink a solution that contains the bacteria under closely monitored conditions.

For the following two weeks we will review you regularly to ask about any potential symptoms or signs of typhoid infection and to make sure you are tolerating the challenge. If you were to develop a fever for 12 hours or more we would treat you with antibiotics that would eliminate the infection. Typhoid fever does not make you very unwell when treated early in this way and it is possible that, with the vaccines used, you may experience only mild symptoms or even none at all. You should be aware, however, that we are giving you a live infection and that you may therefore become unwell (see: **What happens if I get typhoid fever?** below). **ALL** study participants who don't develop typhoid fever will receive antibiotics two weeks after being challenged as a precaution.

The vaccination, challenge and treatment phases of the study will take 10 weeks to complete. After this time we will continue to see you in the clinic intermittently for up to 3 years. **It is essential that you are available for visits in Oxford for the 21 days after challenge.**



*A flowchart giving an overview of what is involved in taking part in this study*

### **Which vaccines are you using in this study?**

Prior to your first study visit, you would be randomly allocated by computer to one of two study arms. One of these arms would be 'double-blinded', which means that neither you nor the study investigators would know which vaccine you have received or been given – you would find this out after completion of the antibiotic course (approximately two months later). Participants in the other arm would be 'unblinded', that is, both they and the study investigators would know which vaccine they have been given at the first visit. Further details about the vaccine arm and the vaccines used are given below.

#### ***Double-blinded arm***

The two vaccines to be used in this arm are:

**M01ZH09.** This is a new, investigational vaccine consisting of a live, attenuated strain of Typhoid bacteria. Specific alterations to the genetic structure of the bacteria prevent it from causing infection in humans while still allowing the body's immune system to develop a protective response against it, thereby preventing future infections. It is therefore classified as a Genetically Modified Organism (GMO) – see [What is a GMO?](#) below. It is an oral vaccine taken as a single dose.

Although investigational, this vaccine has been used in six previous studies involving both adults and children, performed in the UK, US and Vietnam. In all of the studies to-date, there has been no evidence of the vaccine strain circulating in the blood stream (vaccinaemia) and it has been well tolerated by the study participants. Side-effects reported (with a frequency of 5% or more) have included headache, flatulence, abdominal pain, nausea, diarrhoea, asthenia, myalgia, constipation, fatigue, anorexia, pyrexia and musculoskeletal pain. All of these have been mild and self-limiting.

**Placebo vaccine.** The placebo vaccine is identical to the M01ZH09 vaccine but does not contain any active ingredient (i.e. bacteria). It is given in an identical manner and the side-effect profile of the placebo is likely to be similar to that of the M01ZH09 vaccine described above.

#### ***Unblinded arm***

Participants randomly assigned to the unblinded arm would receive a course of licensed Ty21a (trade name: Vivotif ®) vaccine.

**Ty21a.** This is an oral vaccine containing an attenuated strain of Typhoid bacteria. It is widely used, particularly in the US, and is given as an oral capsule on three alternate days. It is generally well tolerated, but 1- 10 % of participants may experience side effects of abdominal pain, nausea, diarrhoea, vomiting, fever, influenza-like illness, headache and rash. Very rarely reported side-effects (less than 1 in 10,000) may include skin reactions, allergic reactions, tiredness, shivering dizziness, numbness and muscle or joint pains.

### **What is a GMO?**

A GMO (Genetically Modified Organism) is an organism, in this case a strain of bacteria, that has had its genetic material altered using genetic engineering techniques. In the case of the M01ZH09 vaccine strain,

two sequences of genetic material (DNA) that are known to be responsible for causing typhoid disease in humans, have been deleted. No new active DNA has been inserted in their place, and the deletions have shown to be stable.

### **What happens if I get typhoid fever?**

The main symptom of typhoid fever is a raised temperature. Some people will also feel tired, have headaches, muscle or joint pains, go off their food, have stomach pain and constipation and/or feel sick. It is really important that we are able to detect if you have a temperature so it is important for you **NOT** to take paracetamol, ibuprofen or any other medication that may artificially lower your temperature.

### **When would you treat me with antibiotics?**

If your temperature goes above and stays over 38°C for 12 hours continuously or if we find any evidence of bacteria circulating in your blood, then we will treat you with effective antibiotics straight away. We know that if we start antibiotics at this very early stage in the typhoid disease process, then you should not become too unwell. However, you are unlikely to feel up to doing much for a couple of days and will probably require bed-rest at home.

Anyone not meeting the criteria for typhoid fever diagnosis by 14 days after challenge will also be treated with a full course of antibiotics.

### **What antibiotics would I be taking and what are the potential side effects?**

All participants will receive an antibiotic called **ciprofloxacin** – this comes as a tablet to be taken twice a day for 14 days. This antibiotic is one of the best treatments for typhoid fever, and is widely used in clinical practice for the treatment of many different types of bacterial infections. Only a very small proportion of people generally experience side-effects from ciprofloxacin; these can include upset stomach, rash, dizziness or itching. Very rarely ciprofloxacin causes sensitivity to sunlight, kidney problems, seizures, problems with your blood cell counts, tendon inflammation or makes people feel confused, depressed or experience hallucinations or other strange sensations. If for any reason you are unable to take ciprofloxacin, there are several other equally effective antibiotics we can use to eradicate the *Salmonella* Typhi.

### **What are the benefits of taking part?**

You may not benefit directly from taking part in this research. You may receive a typhoid vaccine that could prevent you becoming unwell with the infection, either as part of the study or at some future date. We cannot guarantee that you will be protected from typhoid infection however, either in taking part in this study or from future infection.

### **What are the risks in taking part?**

The risks of taking part in this study are very low provided that you return for the follow-up visits; these occur daily for the duration of the challenge (2 weeks). If untreated, typhoid infection can result in serious illness including bleeding from the gut, a hole developing in the gut, becoming a long-term carrier of typhoid, altered consciousness, coma or even death. Long-term carriage of typhoid infection is more likely in

individuals with gall-stones, which is why an ultrasound scan is included as part of the screening procedure.

If you become unexpectedly unwell after challenge then we might ask you to be admitted to the John Warin Ward (an NHS Infectious Diseases and Tropical Medicine Unit) at the Churchill Hospital, Oxford, as a precaution until you had recovered; this is very unlikely to be necessary.

**This is why it is important that you let a study physician know as soon as you develop a temperature or feel unwell and why it is vital that you take the antibiotics as directed.**

In previous typhoid challenge studies performed in the United States, almost 2000 individuals took part, all of whom made a complete recovery from infection.

Typhoid infection is transmitted between individuals principally through poor hygiene practices such as not thoroughly washing your hands after using the toilet and before preparing uncooked food. Most cases of typhoid transmitted in this way occur within the same household; however, transmission is extremely unlikely if good hygiene practices are followed. We will give you detailed advice on how to make sure you don't transmit typhoid to other people and also provide you with liquid soap and disposable towels to help maintain hand washing standards. Additionally, to offer peace of mind to your household and close-contacts, we will offer them voluntary screening to ensure that they have not inadvertently been infected with *Salmonella* Typhi bacteria. If required, this screening would occur after you have started the antibiotic course, but we will provide you with written information when you come for the challenge visit.

***Special cases:***

***Pregnancy.*** Typhoid fever can be particularly dangerous during pregnancy both to the mother and to the foetus. Women will therefore be asked to use an effective method of contraception until the tests show that the *Salmonella* Typhi bacteria has been fully treated. A pregnancy test will be carried out at the screening visit and again before vaccination, challenge and before starting antibiotics.

***Contact with young children and people with immune system problems.*** You should not have contact with children less than 2 years of age or those attending day-care facilities, individuals with immune system problems and the very elderly until we can confirm that you have cleared the *Salmonella* Typhi bacteria in your body. This is because young children and the immunocompromised catch typhoid more easily and become more unwell with it. Please ask if you have further questions relating to this.

***Food handlers.*** Typhoid can be transmitted via 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 medical students).*** If you work in these areas you would have to agree to staying away from your work or studies for the entire challenge period. If you have direct contact with people or patients who are susceptible to typhoid fever or in whom typhoid fever would have particularly serious consequences then you would not be allowed to return to work until three consecutive negative stool samples, obtained one week apart, commencing three weeks after completion of treatment had been obtained. This includes those who are involved in caring for the elderly.

### **Will I be paid to take part?**

Participants will be compensated for travel to the clinic, time and inconvenience caused. Compensation will be paid by cheque *pro rata* for actual visits performed in stages throughout the study, therefore, if you choose to leave the study early or were withdrawn from the study you would be compensated according to the length of your participation based on these figures. Participants completing all study visits will receive approximately £3350 by the end of year 3.

### **Will my taking part in this study be kept confidential?**

All information collected about you during the course of the research will be encoded with a study number and kept strictly confidential. In order to ensure that the study is being conducted correctly, the following groups may inspect the study records and your medical records, without violating your confidentiality:

- Monitors employed to check that the study is being conducted to a high standard.
- Authorised persons from specific regulatory authorities, including the Medicines and Healthcare products Regulatory Agency (MHRA).
- The Clinical Trials and Research Governance Office, University of Oxford, who are responsible for ensuring the appropriate conduct of the research on behalf of the research sponsor (the University of Oxford)

By signing the consent form for this study, you will be giving permission for these groups to look at your medical records; however they would not be able to remove any information that identified you from the premises of the Oxford Vaccine Group. Other groups who would need to be informed of your participation in this study (with your permission) include your General Practitioner (GP), anyone who you live with identified as a close-contact and local public health officials. During the screening visit we will ask you to provide us with your National Insurance or passport number (if you are not entitled to a NI number) so that we can check a national database which helps prevent volunteers from taking part in too many clinical trials. With your consent, we will add your details to this system if you chose to take part in this study.

### **What will happen to the results of the research study?**

The results of this research study may be published in a scientific medical journal. This may not happen until a few years after the study is completed. If you contacted the researchers in the future you could obtain a copy of the results of the research in which you participated. You would not be identified in any report or publication. Parts of this study will also be used in research theses to be submitted by members of the study team.

### **Who is organising and funding this research?**

This research has been designed and organised by the Oxford Vaccine Group, part of the University of Oxford, in collaboration with Emergent BioSolutions, a vaccine development company, and the Wellcome Trust, a medical research organisation. Research funding is from the Wellcome Trust, a medical research charity; the M01ZH09 and placebo vaccine have been supplied by Emergent BioSolutions.

### **Who has approved the research?**

This study is being performed by the Oxford Vaccine Group, part of the University of Oxford, which is acting as the study sponsor. It is being performed with the approval of the Oxfordshire Research Ethics Committee A, the Oxford Radcliffe Hospitals and University of Oxford Genetic Modification Safety Committee, the Department for the Environment and Rural Affairs (DEFRA) and the Medicines and Healthcare products Regulatory Agency (MHRA).

### **OTHER FREQUENTLY ASKED QUESTIONS**

#### **Will having typhoid fever prevent me donating blood to the Blood Transfusion Service in future?**

People who have had typhoid fever diagnosed are not allowed to donate blood in the UK under current regulations. If you do not develop typhoid fever you are not excluded from further blood donation.

#### **What happens to the samples I provide you with?**

The blood, urine, stool and saliva samples collected during this study will be analysed in hospital laboratories at the John Radcliffe and Churchill Hospitals and the Oxford Vaccine Group (part of the University of Oxford). We will also send some samples to other researchers that are working with us on this project, including researchers outside the European Union. We will ask for your permission to use any samples that we take from you that are remaining at the end of this study to help us with other vaccine-related research in the future. This is optional and you may still participate in this study whether or not you let us do this.

#### **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 vaccination and *Salmonella* Typhi 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 typhoid fever.

#### **What is expected of me during the study?**

- You must provide the name and 24-hour telephone number for someone who lives near to you and who will know your whereabouts for the duration of the study.
- You must provide us with the names and addresses of all household close and current sexual contacts so that we can offer them screening for *Salmonella* Typhi infection if required.
- You need to attend all study visits as outlined above and on the study visit card (we would remind you of these!).
- You should record in the study diary given to you any symptoms you notice and your temperature twice a day after vaccination and after typhoid challenge.
- Female participants must use an effective method of contraception until the *Salmonella* Typhi bacteria is cleared from their system – this includes using some form of barrier contraception whilst taking antibiotics and for 7 days afterwards.

**Is there someone I can contact during the study?**

You will have access to a study doctor 24-hours a day until you had been successfully treated for *Salmonella* Typhi infection. It is very important that you stay closely in touch with the study team and let us know as soon as you get a temperature or if you were unwell in any way. If you get any fevers in the first 90 days after challenge we would ask you to call us so that we can arrange to see you and do some stool and blood tests.

**What about private medical insurance?**

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

**What do I do next if I want to take part?**

If you are interested in taking part in this study or have any further questions relating to it, then please contact the Oxford Vaccine Group using the contact details on the cover of this booklet. One of the study team will then contact you to explain the study and answer any further questions. They will also ask about some specific criteria for taking part in the study to see whether there is any obvious reason why it would not be safe for you to take part. If, after this, you were still keen to take part we would invite you to attend a screening visit at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at the Churchill Hospital, Oxford.

**What if I wish to complain or if something goes wrong?**

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 (01865 857420, [andrew.pollard@paediatrics.ox.ac.uk](mailto:andrew.pollard@paediatrics.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 [heather.house@admin.ox.ac.uk](mailto:heather.house@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.

The University has arrangements in place to provide for harm arising from participation in the study for which the University of Oxford is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which you are treated.

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

- We will ring you to check that it is appropriate to include you in the research.
- You would then attend a screening visit at the CCVTM and have an ultrasound scan at the Churchill Hospital to assess your eligibility for the study.
- Following satisfactory screening results you will be asked to come in for (a) vaccination appointment(s). You would be asked to fill in a diary card from day of vaccination to 7 days after the last vaccine dose, to record any symptoms you have and your temperature.

- One month later, you would be challenged with *Salmonella* Typhi by drinking a solution that contains the *Salmonella* Typhi bacteria. You would be asked to fill in a diary card twice a day for 21 days to record any symptoms you have and your temperature.
- You would attend clinic appointments at least once a day for 14 days during which time blood, urine and stool samples would be collected.
- If you were diagnosed with typhoid fever or, if you did not get typhoid fever after 14 days, you would be treated with antibiotics.
- We would continue to see you for the occasional clinic visit for three years after the end of the study.

**Many thanks for taking the time to read this information booklet.**

Yours sincerely,



Prof Andrew J Pollard  
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 Honorary Consultant Paediatrician



Dr. Brian John Angus  
 Clinical Tutor in Medicine  
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