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Volunteer Information Sheet

Lung Innate Immunity and Microbiome after Tuberculosis Exposure (LIMBO-TB)

Thank you for showing an interest in this study. The first page of this information sheet sets out a brief summary. The rest of the document provides more detail. You can ask us for more information at any point.

Condition Studied	Research Study Length	Number of visits
Tuberculosis (TB)	Three months	Three

What will the study involve?

- A screening visit (20-30 minutes) to explain the study and check that you can take part
- Two other visits where you will:
  - Have your blood taken
  - Cough up some samples of phlegm (sputum) after breathing in some salty water (Induced sputum)

Could I be eligible to take part?

You must
- Be aged 18-65 years old
- Never been a close contact with someone with TB
- Be in generally good health

You must not
- Be pregnant or breastfeeding
- Have major breathing problems e.g. severe asthma
- Have had Tuberculosis before

Why take part?

Information gained from this study may help understanding Tuberculosis (TB) infections better, and explain why some people get infected while other do not

There is no known direct benefit to you from taking part in this study.

You will be compensated for your time, travel and inconvenience.

Are there risks?

There are always possible risks with taking part in any study.

Taking blood samples and getting sputum phlegm samples, can be mildly uncomfortable but are not risky procedures

You will not be given any experimental treatments or medicines

Dear Volunteer,

Thank you for showing an interest in taking part in this research study. Before you make a decision, it is important you take the time to understand why the research is being done and what it would involve. Please read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish.

- Part 1 tells you the purpose of the study and what will happen to you if you take part
- Part 2 gives you more information about how we run (conduct) the study, including what happens to samples and the data you provide

Please ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not to take part. **Taking part is entirely voluntary and may withdraw from the study at any time.**

Volunteer Recruitment Coordinator
vaccinetrials@ndm.ox.ac.uk

Contents

Part 1 – What Happens in This Study

1.1 What is the purpose of this study?

We are a tuberculosis (TB) immunology and vaccine research group. We are trying to understand more about why some people get infected when they come into contact with someone with a TB infection while others do not.

TB is a disease caused by a bacteria (*Mycobacterium tuberculosis*). TB disease remains one of the top 10 causes of death worldwide. BCG (Bacillus Calmette-Guerin), given as a single dose under the skin, is the only vaccine currently licenced for use against TB, but it is not always protective. The BCG vaccine works well against disease in childhood, but it is not good enough at protecting against disease in adulthood, which is when majority of TB deaths occur. We are working on developing better vaccines against TB and hope to use what we understand in this study to better protect people.

1.2 Why study people who are close contacts of TB patients?

TB is an infectious disease and worldwide it is estimated that 1 in 4 people are infected. However most infected people with the bacteria causing TB don't get sick, and their bodies are able to fight off the infection or at least keep it at bay. Why some people are able to fight off or control the bacteria is not understood. Other people who come into contact with the TB bacteria don't get infected at all, despite spending a lot of time with someone who is infectious. We suspect that there is something different about the body's immune system which helps to protect some people. If we can understand what this is, we may be able to develop better ways to protect and treat people. Close contacts of those with TB infections are important to study as we know they have had lots of exposure to the bacteria, and allow us to investigate the very early stages of immune response.

Key Concept – What is the microbiome?

The Microbiome is the name given to all of the bacteria that live on and in our bodies. Our skin, guts (intestines), mouth and throat are covered with bacteria all the time. These bacteria don't make us sick and in fact we know that they are good at stopping us from becoming unwell. Changes in people's microbiome has been associated with developing a range of medical problems, although we are only just beginning to understand why and how this happens.

We know that the microbiome is important in 'training' our immune system when we are babies, much less is known about how it effects the immune system during TB infections.

1.3 What will you be looking at in this study?

We are interested in measuring the immune responses to TB in people enrolled in this study. We will collect both blood samples, and also samples of phlegm (sputum). This allows us to explore what is happening in the

lungs as well as the blood more generally. Although the immune system is present throughout our body, we know that there are some cells which exist and respond only in certain parts of the body. From other research involving bacteria similar to TB, we also know that signs of the immune system acting may not be present in the blood even if they are happening in the lungs. As TB infections start in the lungs its important to measure the specific immune responses there.

We will also use the sputum samples to explore your respiratory microbiome. We know that microbiome is different in people who are unwell with TB compared to people who are not infected. But we do not know when these changes happen and whether differences in the microbiome between people helps them to be protected from getting infected in the first place. We will collect samples both from people who have recently had close contact with someone with TB and also people who have never been exposed to TB. The visits are shown in figure 1.

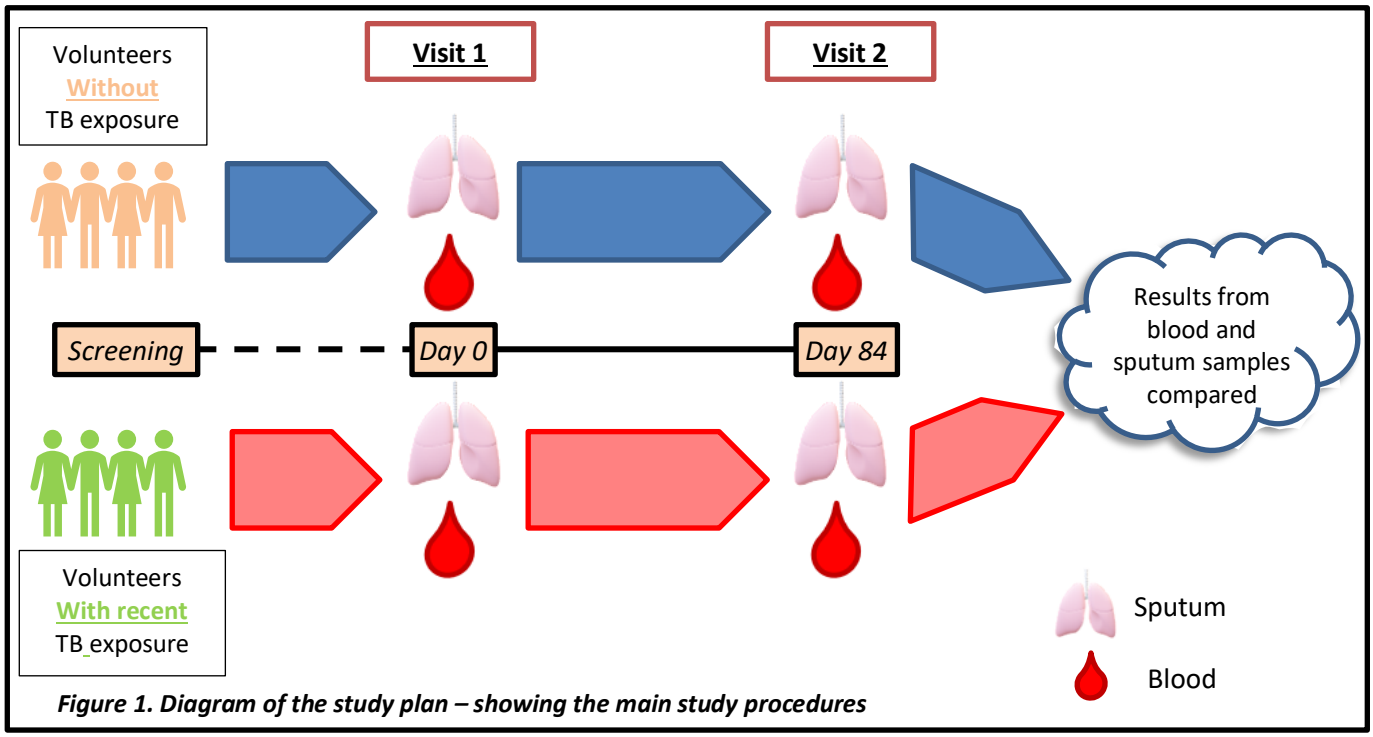

Figure 1. Diagram of the study plan – showing the main study procedures

1.4 What does it mean to have had close contact with someone with TB?

A "close contact" is someone who has spent significant time either living in the same house, or have spent a prolong period of time in the same physical environment (e.g. workplace or social settings) as someone with infectious TB. If you have never been traced by a TB contact tracing team (e.g. NHS of other national healthcare system) you are likely to meet this definition for our study.

1.5 How will I know if I can take part?

As long as you have never had a close contact with someone with infectious TB and are generally well, you are likely to be eligible. If you remain interested after reading this sheet, we will then arrange a time to collect some basic screening information to confirm that you are eligible to take part.

In order to take part in the study you **MUST**:

- Be an adult aged 18-65 years in generally good health.
- Be resident in or near London or Oxford for the duration of the study period
- Be happy to give written informed consent to take part in the study
- Be willing to allow the researchers to review your NHS care record, medical history and blood results and radiographs.
- Be able and willing (in the researcher's opinion) to comply with all study requirements including blood tests and induced sputum procedure.

You **CANNOT** take part in this study if:

- You have lived or had close contact with anyone with TB or have been offered screening for TB through NHS or other healthcare systems at any point in the past
- You have a significant history of allergies or severe allergic reactions, including to any medications including anaesthetics that are required during the study
- You have any significant problems with your immune system or you have HIV
- You have previously been diagnosed or treated for TB disease
- You have previously been diagnosed with latent TB infection or have previously had positive test for latent TB (including an IGRA test or positive TB skin test)
- You have been told by the TB clinic that you have active TB disease of evidence or this on chest X-ray or other tests undertaken by the TB clinic.
- You have ever received an experimental TB vaccine or had aerosolised BCG in the past
- You are taking any tablet or inhaled steroid medication or other drugs working on your immune system or have done so for more than 14 days in the past 6 months
- You have had immunoglobulins or any other blood products (such as blood transfusion) in the 3 months before your involvement in this study
- You have a history of cancer (except basal cell carcinoma or carcinoma in situ)
- You have a history of significant drug or alcohol abuse
- You have taken antibiotics in the last 4 weeks
- You are pregnant, breast-feeding or trying to become pregnant during the study
- In the last 30 days you have taken part in, or plan to take part in, another study of an investigational (experimental) product at the same time as this study
- Any significant abnormalities in the screening lung function tests done at the time of screening.
- Any other significant disease, disorder, or finding, which, in the opinion of the researcher, may either put you at risk, affect your ability to participate in the study or make it difficult to interpret the study data

1.6 Do I have to take part?

No, taking part is entirely voluntary. It is up to you to decide whether or not to take part. Your decision will not result in any penalty, or changes to your standard medical care. If you do decide to take part, you will be given this information sheet to keep (or be sent it electronically) and will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason.

The University of Oxford does not urge, influence, or encourage any employees or students of the institution to take part in this research study. Your decision to not take part in the study, or a decision on your part to withdraw from the study, will have no effect whatsoever on your employment/student status at the University if applicable.

1.7 What will happen if I decide to take part?

If you decide you would like to take part in this study, you will need to attend a brief screening visit lasting approximately 30-40 minutes. The screening visit and all follow-up visits will take place in the XXXX.

At the screening visit, you will be met by one of the investigators (researchers) who will go through this information sheet with you to ensure that you understand what to expect, the risks involved and what side-effects you might experience. You will also have the chance to ask any questions that you might have about any aspect of the study.

Once you feel that you understand what the study involves, and the investigator is satisfied that you have understood everything, you will be asked to sign a consent form that will be kept at the study site. You will be given a copy of this consent form to take away and keep.

Having signed the appropriate forms, the investigator will go through a few questions for administrative purposes and detailed questions related to your health. This will be followed by a brief medical examination of your skin including looking for evidence of a previous BCG scar, heart, lungs, abdomen and glands. We will record your weight and height. To check that your lungs are healthy, we will measure your lung function. The lung function test is done by taking a deep breath and then breathing out through a mouthpiece attached to a machine which gives us readings. (see Photo 1)

If you are eligible, we will let you know that you are eligible and you may either have your blood and sputum samples taken immediately or asked when would be a convenient time to return for testing.

Photo 1. Breathing into a lung function machine. Lung function tests are done at the screening visit and during induced sputum

1.8 What will happen at the study visits?

You will have two study visits, an initial visit and then another visit 3 months later. At each visit we will collect some information about any recent antibiotics or other medication and about your general health. We will also take blood tests and obtain samples of sputum (phlegm). To help you cough up samples of sputum we will ask you to breath in a fine mist (aerosol) of salty water which will loosen phlegm from your chest and help you to cough, in a procedure called induced sputum.

1.9 What will happen if I want to leave the study after I start?

Taking part in the study is entirely voluntary. You have the right to withdraw at any time. Additionally, volunteers may rarely be withdrawn from the study at the discretion of the investigator. This may be due to:

- concerns for the volunteer's health and well-being
- ineligibility discovered during the study or retrospectively
- significant changes from the study procedures
- volunteer non-compliance with study requirements
- confirmed pregnancy during the study.

The study may be put on hold for any event(s) that may risk the safety of volunteers or the reliability of the data.

1.10 What should I avoid during the study?

You should not take part in other studies that involve blood sampling or the administration of drugs or vaccines. If during the study you require any vaccinations for health, travel, or occupational reasons, you should inform the investigators who can advise you if and when it is safe to receive them.

Any volunteer who becomes pregnant during the study should immediately tell their research doctor. If you were to become pregnant, we would not routinely take blood from a pregnant volunteer unless there is clinical need.

1.11 Are there any risks from taking part in the study?

The risks and side effects of the study procedures are detailed here:

Blood samples

Taking blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. Very rarely, blood taking can cause soft tissue infection to develop. During the course of the study we will need to take up to a maximum 62.5ml of blood at a single visit. We take around 125 mls during the study which is significantly less than during a blood donation.

Lung function test

This is a very safe test, which sometimes causes a short period of lightheadedness or coughing as you breathe out vigorously into the mouthpiece. The gases you will be asked to breathe in are harmless at the low levels used.

Throat Swabs

If we are unable to obtain enough sputum we may take a throat swab instead. These are not painful but can be uncomfortable. Swabbing the back of the throat can cause individuals to cough or gag.

Induced sputum

This is a simple and safe procedure. You will be asked to breathe in a fine mist (aerosol) of salty water, this causes you to cough and helps bring up phlegm. (photo 2) For some people this may lead to coughing spasms. If this happened, you would be asked to stay in clinic until any coughing stops. Very rarely the salty saline may cause your airways to spasm. This is extremely unlikely in people with no history of asthma and is quickly reversible with medication. A sensation of shortness of breath may rarely be experienced during induced sputum procedures.

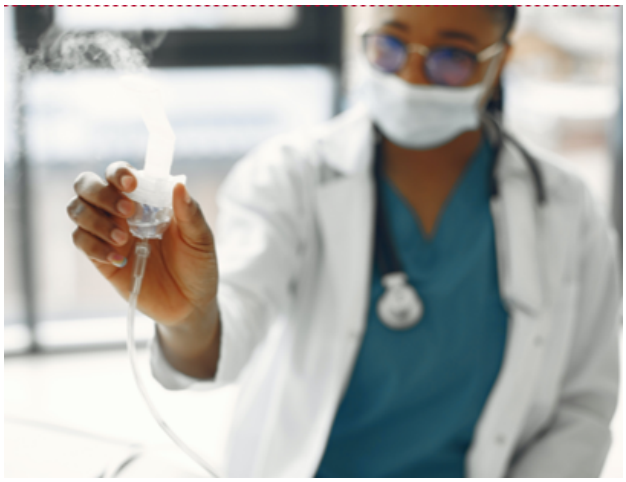

Photo 2. Nebulizer device which turns salty water into a fine mist used during the induced sputum

1.12 What are the possible benefits of taking part?

You will not necessarily gain any direct benefit from the study. During pre-study assessment you will get information about your general health and lung function measurement. However, these assessments are not carried out for diagnostic purposes and should not be considered a substitute for a doctor's visit.

Information gained from this study may aid in the development of more effective vaccination programmes to prevent TB worldwide.

1.13 Will my General Practitioner/family doctor (GP) be informed of my wish to take part?

As part of the consent process, you will be asked to allow the investigators to contact your own doctor (GP) to obtain your medical information if we think this is needed. We may do this to ensure that there are no medical reasons why you should not take part. We will not routinely contact your GP to tell them that you are taking part in this study unless you ask us to do so , in which case we would use an encrypted NHS email address to contact them.

If we found significant abnormalities during your examination or in your lung tests, this will mean you cannot take part. If we thought it was an important finding we will ask your permission to contact your GP or a specialist doctor, whichever is the most appropriate, to ensure the abnormality is followed up. *At no point will your test results be divulged to anyone outside the study team without your permission.*

1.14 Will I be reimbursed for taking part?

You will be compensated for your time, inconvenience and travel expenses. You are not anticipated to incur any additional expenses due to your involvement in the study. We will reimburse you £50 for each of the two study visits (total £100) for your participation in the study.

Study reimbursement will be made by bank transfer, usually within six to eight weeks of you completing the study. Please bring your bank details with you to your screening visit; no cash payments can be made. Should you decide to withdraw from the study before it is completed, you will receive a proportion of the total amount based upon the parts of the study you have completed.

We will not pay tax or National Insurance from the money due to you. It is your responsibility to pay these and to check how any compensation received from taking part in the study affects any state benefits to which you are entitled. Contact HM Revenue & Customs for information (http://www.hmrc.gov.uk/ or telephone 0300 200 3300).

Please note that there are some situations where we are required to tell the authorities about your payments

if we are asked to.

Part 2 – How the Study is Conducted

2.1 What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue, you would be asked to sign an updated consent form. Upon receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study.

2.2 What will happen if I don't want to carry on with the study?

Taking part is entirely voluntary and you are free to withdraw at any time, without needing to provide a reason. If you withdraw, we would not perform any more research procedures. With your permission, we would like to store the samples already collected but if you did not want this, we would discard them. Please note that if samples have already been used in research testing, they cannot be withdrawn and any resulting data will be retained. If you choose to withdraw from the study, your standard medical care will not be affected.

2.3 What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your taking part in this study. In the event that something does go wrong and you are harmed during the research, and this is due to someone's negligence then you might have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. At any time during the study, you will be entirely free to change your mind about taking part, and to withdraw from the study. This will not affect your subsequent medical care in any way.

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 can contact the Chief Investigator, Professor Helen McShane on 01865 617973 or helen.mcshane@ndm.ox.ac.uk. Alternatively, you may contact the University of Oxford Research Governance, Ethics and Assurance Team (RGEA) office on 01865 616480 or the director of RGEA via email: RGEA.complaints@admin.ox.ac.uk.

2.4 What tests will be done on my samples?

The immunology blood tests (62.5 ml at each visit) will look at your body's response to TB bacteria. In the sputum (phlegm) samples, we will look to see if the immune system response specific to the lungs has been triggered and measure the normal bacteria (microbiome) of the airways to see whether it changes in people who have come into contact with TB.

The samples will be processed either at University College London or at the University of Oxford. Some samples may be transported for processing in collaborating research centres in the UK or EU. All samples will remain pseudonymised throughout – this means that although samples will not have your personal details directly attached to them, it would be possible for members of the study team to link them back to the correct volunteer if necessary. The link to your personal details will not be available to anyone other than the clinical members of the team.

2.5 What will happen to leftover samples?

If you consent, your leftover samples may be stored indefinitely at the Oxford Vaccine Centre Biobank and may be used for further related research, including into tuberculosis, the human body's immune response, vaccine research and/or your safety. More information around the procedures for long-term storage of your samples is available in the Oxford Vaccine Centre Biobank information booklet and you will be asked to sign a separate biobank consent form if you agree. Your involvement in this study will not be affected by your decision regarding storage and future use of your leftover samples in the biobank.

2.6 Will any tests be done on genetic information?

We may try to identify and study the genes that appear to be important in response to the *M.tb* bacteria or in protecting against TB. We will only look at specific areas of interest, not your whole set of genes. We will not

perform analysis called whole genome sequencing on fresh or stored biospecimens. Samples will be tested in anonymised form; however, your DNA is unique to you so it can never be completely anonymous.

2.7 Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the study will be kept strictly confidential. Blood and sputum sample will be processed under a pseudonymised study number. Some of this pseudonymised research data may be shared with other collaborating researchers at institutions outside of the UK so that the samples can be processed. However, we will not share identifiable personal information with them. Responsible members of the University of Oxford and the relevant NHS Trust(s) may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. We will not routinely tell your GP about your involvement in the study, but can do so if you would like us to. Every effort will be taken to maintain confidentiality. Information about you may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the research site.

2.8 What will happen to my data?
The University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. We will be using information from different sources including you, your hospital or GP records in order to undertake this study and will use the minimum personally-identifiable information possible.

We will store any research documents with personal information, such as consent forms, securely at the University of Oxford for 5 years after the end of the study.. Once the study has been completed, all documents would be archived in a secure facility.
If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form securely until such time as your details are removed from our database. We will keep the consent form and your details separate from one another and any research data.

Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at [https://compliance.web.ox.ac.uk/individual-rights]. You can also find out more about how we use your information by contacting the Chief Investigator – helen.mcschane@ndm.ox.ac.uk.

2.9 Who is organising and funding the research?
This study is funded by the Medical Research Council, through a Clinical Training Research Fellowship awarded to Dr Timothy Fredsgaard-Jones to fund research which will be used to complete his PhD. The study is designed and organised by the investigators. Neither your hospital nor the researchers are paid for recruiting you in this study.

2.10 Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect volunteers' interests. This study has been reviewed and given favourable opinion East of England – Essex Research Ethics Committee (Ref: 24/EE/0070)**.**

2.11 What will happen to the results of the research study?
The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until one or two years after the study is completed. A lay summary of published reports will be available on request via email, to all study participants for their information and interest. We are not able to provide individual results to volunteers. You will not be identified in any report or publication. Data from this study may be used as part of a student post-graduate degree, for example an MD or DPhil. The pseudonymised data from this study will be shared with our collaborating partners who are organising and funding this research. Data from this study may be used to file patents, licence vaccines in the future or make profits in other ways, this will not contain any identifiable data about you. You will not be paid for any part of this.

2.12 Will you contact me about other research studies?

As part of the consent process, we will ask if you would allow us to keep your contact details beyond the end of the study to let you know about other research studies we are completing. This is entirely optional and your participation in this study will not be affected by your decision.

If you consented, your details would be stored electronically on a secure server and only authorised individuals at the University of Oxford and site-specific study teams will have access to it. We will not, under any circumstances, share your contact details with any third party institutions without your permission. Being contacted about future studies does not oblige you to agree to take part in future research and you can ask us to have your contact details removed from our database at any time.

2.13 Further information and contact details

Thank you for your interest in the study, we hope this information sheet has answered all of your questions. If you would like further information about taking part in research please visit the following website: [http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx]. For independent advice about taking part in this study you may wish to contact your GP. If you would like to speak to one of our study doctors or Professor Helen McShane (Chief Investigator) to discuss any aspect of this study, or if you would like to take part in this study, please contact:

Volunteer Recruitment Coordinator, Centre for Clinical Vaccinology & Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE Telephone: 01865 611424 Email: vaccinetrials@ndm.ox.ac.uk