Volunteer Information Sheet

Studies of TB vaccines in healthy adults

TB038: Evaluation of the heterologous effects of Bacille Calmette-Guérin (BCG) vaccination in healthy UK adults

Reviewed by NHS Research Ethics Committee (reference number: 15/SC/0022)

Dear volunteer,

Thank you for showing interest in this clinical study. Before you decide whether to take part, it is important for you 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. Please ask us if there is anything that is not clear or if you would like more information.

- Part 1 tells you the purpose of the study and what will happen to you if you take part.
- Part 2 tells you more information about the conduct of the study.

Part 1

What is the purpose of the study?
Tuberculosis (also known as TB) is a disease caused by bacteria that continues to be a significant cause of death worldwide. BCG (Bacille Calmette-Guérin) is the only vaccine currently in use against TB. BCG works well against disease from TB in childhood, but it is not good enough at protecting against disease in adulthood. Steps are in place to develop a replacement vaccine for BCG. However, when babies are given BCG in the first few weeks of life, it has been observed that these babies appear to be protected against death from infections caused by other types of bacteria, not just TB. Our understanding of how this protection occurs is not complete. We want to gain a better understanding of how the body’s immune system reacts to BCG and in turn potentially prevents infection from other bacteria.

What is BCG?
BCG is a strain of the bacterium that causes TB in cattle. It is a live vaccine, meaning the bacteria in the vaccine are still alive but are weakened so that they improve the body’s immune system response against TB, but do not cause TB disease.

BCG SSI is the type and strain of BCG used routinely for vaccination in the UK. Due to global demand, it can often go into short supply. Should this happen then an alternative BCG vaccine with WHO pre-qualification will be used. This will use a slightly different strain of BCG.
Is BCG safe?

BCG is one of the most widely used vaccines in the world. Three billion people have been given the vaccine over the past 90 years and no serious side effects have been seen in healthy people.

Can I take part?

If you are aged between 18 and 45 years, live in or around Oxford or Birmingham, are in good health, have never been immunised with BCG and have not participated in a clinical trial where TB trial vaccines have been used before, you may be eligible to participate. Conditions such as asthma that are well controlled would not automatically exclude you from participating, however if you are taking long term antibiotics for any reason you may not be able to participate. You must be able to comply with all of the study requirements and be able to attend all of the follow up visits. Participation is voluntary and at the discretion of the investigators and you are free to withdraw at any time. Women who are pregnant or who are trying to become pregnant should not take part in this study. Those with a history of allergy to other vaccines may not be able to participate.

What will happen if I decide to take part?

If you decide to take part in this study, you will need to attend for a screening visit. The screening visit will take place at your nearest clinical site (either the National Institute for Health Research Wellcome Trust Clinical Research Facility (NIHR WTCRF), The Queen Elizabeth Hospital, Birmingham, or the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford). At your screening visit you will meet one of the Investigators who will go through this information sheet with you to ensure you understand what to expect by taking part, the risks involved and what side effects you can expect to experience. All subsequent visits as outlined in the following section will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford or John Warin Ward, Churchill Hospital, Oxford.

Once you are happy that you understand what the study involves, and the Investigator is happy you have understood everything, you will be asked to sign a consent form. You will be asked permission for the Investigators to contact your GP to make sure there are no medical reasons why you should not participate. You will also be asked to agree to being registered (using your National Insurance number or passport number) on the confidential TOPS (The Over-volunteering Prevention System) database which is set up to prevent people entering into multiple studies at once.

The Investigator will go through a few questions for administrative purposes and detailed questions relating to your health. This will be followed by a medical examination of your skin, chest, abdomen, and the lymph glands in your upper body. Your blood pressure, pulse, temperature, height and weight will also be recorded. You will be asked to provide a urine sample and for women a urinary pregnancy test will be performed. You will have a swab taken from your nose.

A number of blood tests will also be carried out, including tests that look at your kidney and liver function and tests to see if you have been exposed to HIV, Hepatitis B or Hepatitis C. In the event of you testing positive to any of these infections, we would inform you of the result and, with your permission, offer referral for medical review, confirmation of the result, and treatment if necessary. The swab taken from your nose looks for a skin bacteria called *Staphylococcus aureus*. This common bacteria is found in approximately 30-60% of people and is therefore considered normal.

Once all your test results have been checked and there are no problems, you will be contacted to arrange a date to start the study. There is a chance that you will be found unsuitable for the study during your screening. If this is the case, we will inform you of the reasons why.

Sometimes the test results do not fall within the usual ranges for healthy individuals. In this case, you would be asked to return for a repeat test so that it can be checked again. If the test results are still out of range, this will mean you will not be able to participate and we will ask your permission to contact your GP or a specialist doctor 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.

Occasionally with our screening tests we discover evidence of inactive TB bacteria present in the volunteer’s body even though they have no symptoms. This is *not* active TB disease; it is known as latent TB infection. If
this happens you would be excluded from the study and we would organise some further tests including specialist follow up.

**How is the study going to work?**

For this study we plan to recruit 40-48 people and split them into two groups (those who will receive BCG and those who will not). 32 volunteers will be randomised to receive BCG vaccination at the standard vaccination dose. 8-16 volunteers will be randomised to take part as controls; they will not receive BCG vaccination but will be asked to submit blood samples. Volunteers will be allocated to a group at random and so will not be able to choose which group they are in for this study.

Those who are in the group which receive BCG will be given it as an intradermal injection. This means that the vaccine is injected with a tiny needle into the superficial layers of the skin, usually of the upper arm. For women a pregnancy test will be performed before the vaccination.

All volunteers will be asked to return for a series of follow up appointments in order to allow the study Investigators to obtain a blood sample. Volunteers from Oxford will have a total of 9 visits (excluding the screening visit) over a period of three months, and volunteers from Birmingham will have 7 visits (excluding the screening visit). The schedule for the vaccination and follow up visits is shown in the diagram below. All visits (excluding the screening visit) will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford for both Oxford and Birmingham volunteers to ensure minimal delay for blood being taken to arrive at the Oxford laboratory for processing. Transport in the form of a taxi will be arranged for those volunteers travelling from Birmingham to Oxford.

At each visit you will be asked a few questions to check there have been no new problems since the last visit including any illness/infection which might require you to take a course of antibiotics. If this happens it will not stop you from continuing to take part in the study, but the investigator may delay your visit for blood sampling. For those who receive BCG we will check the vaccination site. All volunteers will have a blood sample taken at each visit. Swabs from your nose will be taken at 2-3 of your study visits. Prior to you Day 0 visit you will be provided with the necessary equipment and instruction on how to obtain your faecal sample. You will be asked to bring this sample with you to your Day 0 visit. This is assessing for different types of normal bacteria that can be present in your stool. You may be asked to repeat this on Day 7 and Day 14 depending on the results of your first sample.
On the vaccination visit you will be required to wait for 15-20 minutes after having the BCG injection. This is to ensure that you are well after vaccination. You will be reviewed at the end of this time period and allowed to go home as long as you are well.

**What should I avoid during the study?**
You should not give blood during the study or 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 will decide if and when it is safe to receive them.

Women should use an effective contraceptive method (such as the oral contraceptive pill, a contraceptive hormonal implant, an intra-uterine device, or condoms) for the whole of the study. Even though no harmful effects of BCG vaccination on the fetus have been observed, there have not been studies to prove its safety. Pregnant women therefore must not take part in this study; neither should women who plan to become pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part and prior to receiving the vaccine to exclude the possibility of pregnancy. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor. If you were to become pregnant, any baby born may need to be followed up.

**Will I be paid for taking part in this study?**
You will be compensated for your time, the inconvenience of having blood tests and procedures, and your travel expenses. The total amount compensated for volunteers from Oxford will be approximately £320. Due to the increased travel time, volunteers from Birmingham will be compensated approximately £440.

Payment will be made by BACS payment within 6 weeks of your final study visit. Please ensure that you bring your bank details with you to your screening visit. Should you decide to withdraw from the study before it is completed, payment will be *pro rata* (you will only receive a proportion of the total amount which will be reflective of the number of visits you attended).

**Are there any risks from taking part in the study?**
The risks and side effects of the proposed study procedures are detailed here:

*Blood samples*
Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Occasionally more than one attempt is required to obtain a blood sample. Rarely, people feel light-headed or even faint. During the course of the study we will need to take between 59.5mL and 68mL of blood (approximately 4 tablespoons) at a single visit. The total amount we will take over the period of the study is no more than 565mL for Oxford volunteers and 446mL for Birmingham volunteers. As a comparison, if you were to donate blood to the National Blood transfusion Service, you would have approximately 470mL of blood taken during a single visit. National recommendations are that men donate no more than every 12 weeks and women every 16 weeks. For that reason we ask you to refrain from blood donation for a period of 3 months after your final study visit. You can return to blood donation after this period of time should you wish.

*Nasal swabs*
This is a painless and safe procedure.

*Faecal sample*
This is a painless procedure which you can perform yourself. You will be given appropriate instruction and provided with the necessary equipment to safely collect the specimen.

*Intradermal injection with BCG*
The most common side effects from intradermal injection are superficial discomfort at the injection site with swelling and redness that can last a few days. A small ulcer usually forms about a week later at the site of the injection. This usually heals over a few weeks to months and leaves a small flat scar. It is also possible to develop some swelling of glands in the armpit, but usually less than one centimetre across.
Uncommonly (happens to less than one in a hundred people) swelling of glands in the armpit of more than 1cm across, or an ulcer that leaks fluid at the injection site may occur. If this happens, the ulcer should be allowed to dry, and tight clothes should be avoided. Occasionally antibiotics may be required. Other symptoms that occasionally occur after BCG include headache or a low grade fever.

Rare side effects (happens to less than one in a thousand people) include more severe inflammation of glands leading to abscesses. Theoretically, infection with the bacteria in the vaccine can spread through the body, including to the bones. However this is extremely rare in people who are otherwise healthy. This would need to be treated in a similar way to the treatment of TB.

As with all vaccines and medicines, there is a risk that you may have an allergic response to the vaccine. In the instance of an allergic reaction, including anaphylaxis, we have the necessary medications and equipment to treat you. It is for this reason that we observe you for 15-20 minutes after vaccination with BCG.

If you experience unexpected events or become concerned during the study you can call the emergency contact number given to you at enrolment. A qualified study doctor is available at all times on this number.

What are the advantages of taking part?
There is no direct benefit to you from participating in this study, however, during pre-study assessment you will get information about your general health. Information gained from this study may aid in the global approach to infant vaccination programmes and improve our approach to vaccine development.

Part 2

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. Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study.

What will happen if I don’t want to carry on with the study?
Participation is voluntary and you are free to change your mind and withdraw at any time. You do not need to provide a reason. This will not affect your subsequent medical care in any way. If you withdraw we might need to offer you a follow up visit, to check the vaccination site or a blood result for example.

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

If you wish to complain about any aspect of the way in which you have been treated during the course of this study, you should contact the Chief Investigator, Professor Helen McShane, on 01865 617606 or helen.mcshane@ndm.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or ctrg@admin.ox.ac.uk.

Would 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. It is available only to the study team, regulatory agencies, the Sponsor (University of Oxford) and the funder (The Gates Foundation and The Wellcome Trust). Responsible members of the University of Oxford and/or NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. They are bound by the same confidentiality rules. Your GP will be informed about your participation, as mentioned in part 1. Any information about you that leaves the hospital/clinic will be anonymised through the use of a special volunteer number which will be specific to you. Information about you will be stored electronically on a secure server using your unique volunteer number, and paper notes will be kept in a locked filing cabinet at your local site. Your bank details will be held on a secure electronic
database in order to process BACS transfer of your compensation. Your bank details will be held for the duration of the study and then destroyed.

Study results
When the study results are published this scientific paper, together with a layperson summary, will be sent to you.

What tests will be done on my blood samples?
The blood tests we perform include tests for blood cell count, how your liver and kidneys are functioning, your immune response to TB or BCG, and if you have been exposed to HIV, Hepatitis B or C. We will do genetic tests on your blood samples to look at the genes that regulate your immune response. We may also try to identify and study the genes that may be important in response to vaccination or in protecting against TB.

With your consent some of your leftover blood samples will be stored and may be used for further studies concerning BCG specific or other vaccine related responses. These will have ethical approval from the appropriate ethical committee. Samples will be stored indefinitely and may be passed in an anonymised form to the funders listed above. Upon your request at any time, your remaining blood samples will be destroyed.

What tests will be done on my other samples?
Your urine sample will be used to check your kidneys are functioning normally. For women we will also test if you are pregnant. Your urine will not be stored. Nasal swabs will be tested to see if you have normal bacteria called Staphylococcus aureus. Your faecal (stool) samples will be tested to see if you have bacteria called Escherichia coli, Klebsiella pneumoniae, or Group B streptococcus. These bacteria are often present in healthy people’s faeces and this is not harmful to you. With your consent some of your leftover nasal and faecal samples will be stored and may be used for further studies concerning BCG specific or other vaccine related responses. These will have ethical approval from the appropriate ethical committee. Samples will be stored indefinitely and may be passed in an anonymised form to the funders listed above. Upon your request at any time, your remaining samples will be destroyed.

Who is organising and funding the research?
This study is funded by The Gates Foundation and The Wellcome Trust. It is designed and organised by the Investigators. Neither your GP nor the researchers are paid for recruiting you in this study.

Who has reviewed the study?
This study has been ethically reviewed by NHS Research Ethics Committee (Reference number: 15/SC/0022).

Further information and contact details
We hope this information sheet has answered all of your questions. If you would like further information about participating in research please visit the following website: http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx. For independent advice about participating in this study you may wish to contact your GP. If you would like to speak to 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:

Recruitment Coordinator
Centre for Clinical Vaccinology & Tropical Medicine
Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Telephone: 01865 857406
Email: vaccinetrials@ndm.ox.ac.uk

If you have any medical problems during your participation in this study please contact 01865 857476 or 01865 857401 (9am-5pm Mon-Fri), or 07917 882967 (24 hour emergency number). Alternatively, if your query is not urgent you can email vaccinetrials@ndm.ox.ac.uk