Challenge Non-Typhoidal *Salmonella* (CHANTS) Study

The Development of a non-typhoidal *Salmonella* human challenge model: A safety and dose escalation study.

Participant Information Sheet

We would like to invite you to take part in this new research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you.

Please read this Participant Information Sheet carefully. A member of the study team will then go through this information sheet with you and answer any questions you may have. Please talk to others, including your family and friends about the study if you wish. You do not have to take part in this study, and you can change your mind at any time.

Thank you for taking the time to consider taking part in this study.

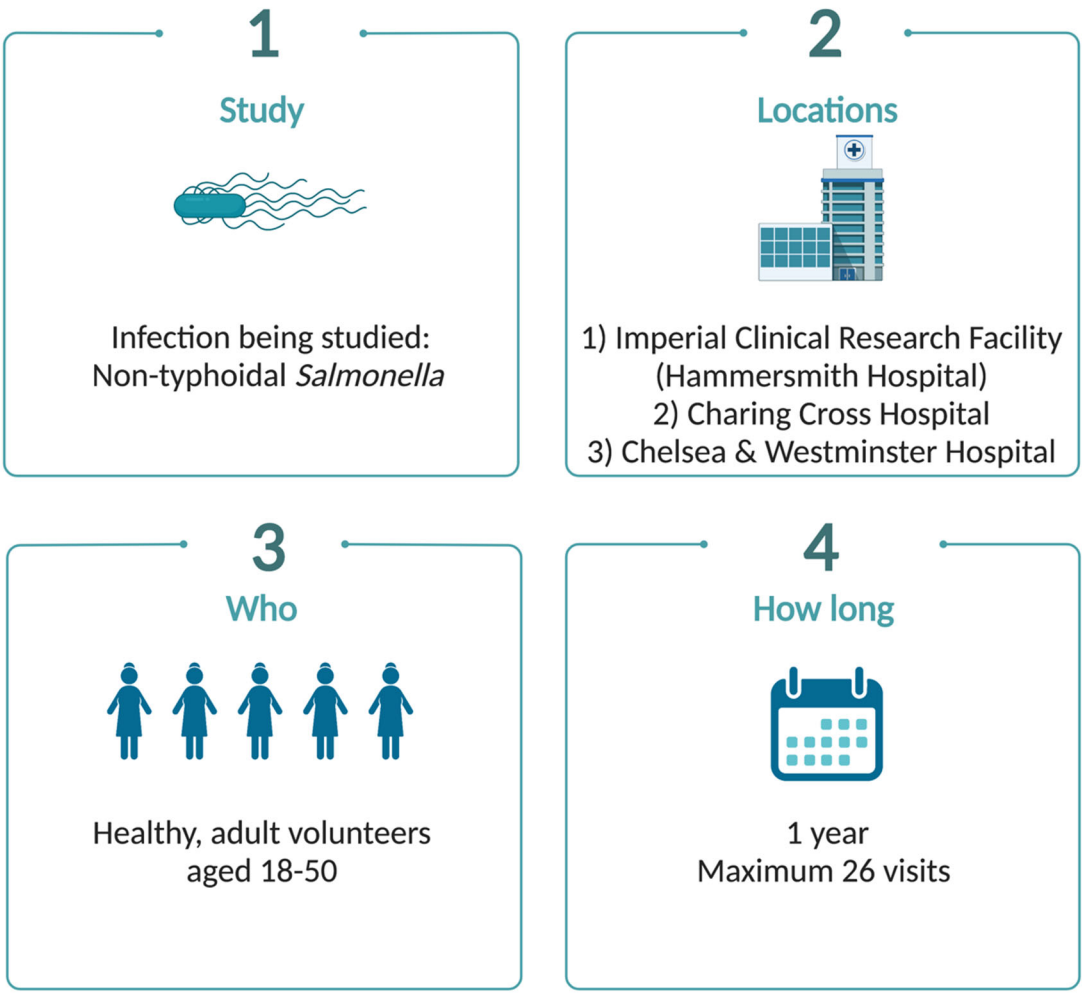
Sponsor: Imperial College London
Sponsor reference: 21HH6989
IRAS Project ID: 301659
Research Ethics Committee: London - Fulham
Research Ethics Committee Reference: 21/PR/0051
Study Funding: The Wellcome Trust (Reference UNS127883)

Chief Investigator: Dr Malick Gibani, Department of Infectious Disease, Imperial College London
Co-Investigators: Professor Christopher Chiu, Professor Graham Cooke, Department of Infectious Disease, Imperial College London
Study Sites:

1. Imperial College Healthcare NHS Trust
    a. NIHR Imperial Clinical Research Facility, Imperial College Healthcare NHS Trust, Hammersmith Hospital Campus, Du Cane Road, London, W12 0HS
    b. Ward 15S, Charing Cross Hospital, Imperial College Healthcare NHS Trust Fulham Palace Road, London, W6 8RF
2. Chelsea and Westminster Hospital NHS Foundation Trust
   Chelsea and Westminster Hospital
   369 Fulham Road
   London
   SW10 9NH

Contact Details: Email: chants@imperial.ac.uk Telephone: 07894986332

KEY SUMMARY OF THE STUDY



If you decide to take part in the *Salmonella* (NTS) challenge study:

- You would be 'challenged' (deliberately infected) with one of two strains of a bacteria called ***Salmonella* Typhimurium.** This belongs to an important group of bacteria called non-typhoidal *Salmonella* (NTS). This group of bacteria usually causes diarrhoea and gastroenteritis.
- Before enrolling in the study, you would need to attend for screening tests (including a medical history, physical examination, blood and urine tests, an ultrasound of your abdomen and a heart check (ECG)) to ensure you are suitable to take part.
- You would need to fast (not eat or drink except for water) before certain appointments:
    - 6 hours before an ultrasound scan during the screening tests (6 hours)
    - 1 and a half hours before being challenged with *Salmonella* (NTS).
- You will be challenged with live *Salmonella* (NTS) under medical supervision, by swallowing a drink that contains a defined amount of the bacteria.
- After being given the bacteria, you will be admitted to a hospital room.
    - You will stay in quarantine on your own in a single, en-suite room for around 7 days.
    - During this time, we would collect a daily blood sample and daily stool (poo) samples.
    - **If there is a risk that you are still contagious (i.e., if you could infect someone else), you may have to stay longer.**

        - **In practice, this means that you have to be free of diarrhoea for at least 48 hours before leaving the quarantine facility.**
        - **This would usually be only a few more days at most.**
    - A small number of visitors will be allowed, but they would have to comply with a strict hygiene protocol.
    - You can bring in personal devices such as phones, laptops and tablets to watch films, study, work, and to call friends and family.
- We would ask you to record all your symptoms and diet in a diary.
- After the quarantine period has ended, you would need to attend daily visits for a further 7 days, where we would collect blood and stool (poo) samples.
- You are likely to develop symptoms of *Salmonella* (NTS) infection, including:
    - Diarrhoea
    - Stomach-ache
    - Fever
    - Vomiting

  These symptoms would mostly get better after a few days – usually between 3 to 7 days – but in rare circumstances may last longer.
- There is a very small risk of a more severe illness, but this is extremely rare in young, healthy people.
- You would be offered antibiotics to make sure the infection is cleared up.
- You will need to stay in close contact with the study team until you have completed the course of antibiotics.
- You would need to provide 3 stool samples after finishing the antibiotics so we can make sure you are clear of infection.
- After finishing the antibiotics, you would be asked to attend for a further four visits over the next year.
- You will be compensated up to £3237 for your time and expenses (such as travel) if you attend all study visits.
- You may be asked to attend additional follow-up visits for safety monitoring. You will be reimbursed for any extra visits.
- You would be given an emergency telephone number and other contact details for the study team in case you have any questions or concerns at any time.
- You would have to inform your household and close contacts if you decide to take part. We would offer them screening for *Salmonella* (NTS) infection.
- Female participants should use an effective method of contraception until they are cleared of *Salmonella* (NTS) bacteria, including barrier contraception whilst taking antibiotics.
- The study is funded by the Wellcome Trust.

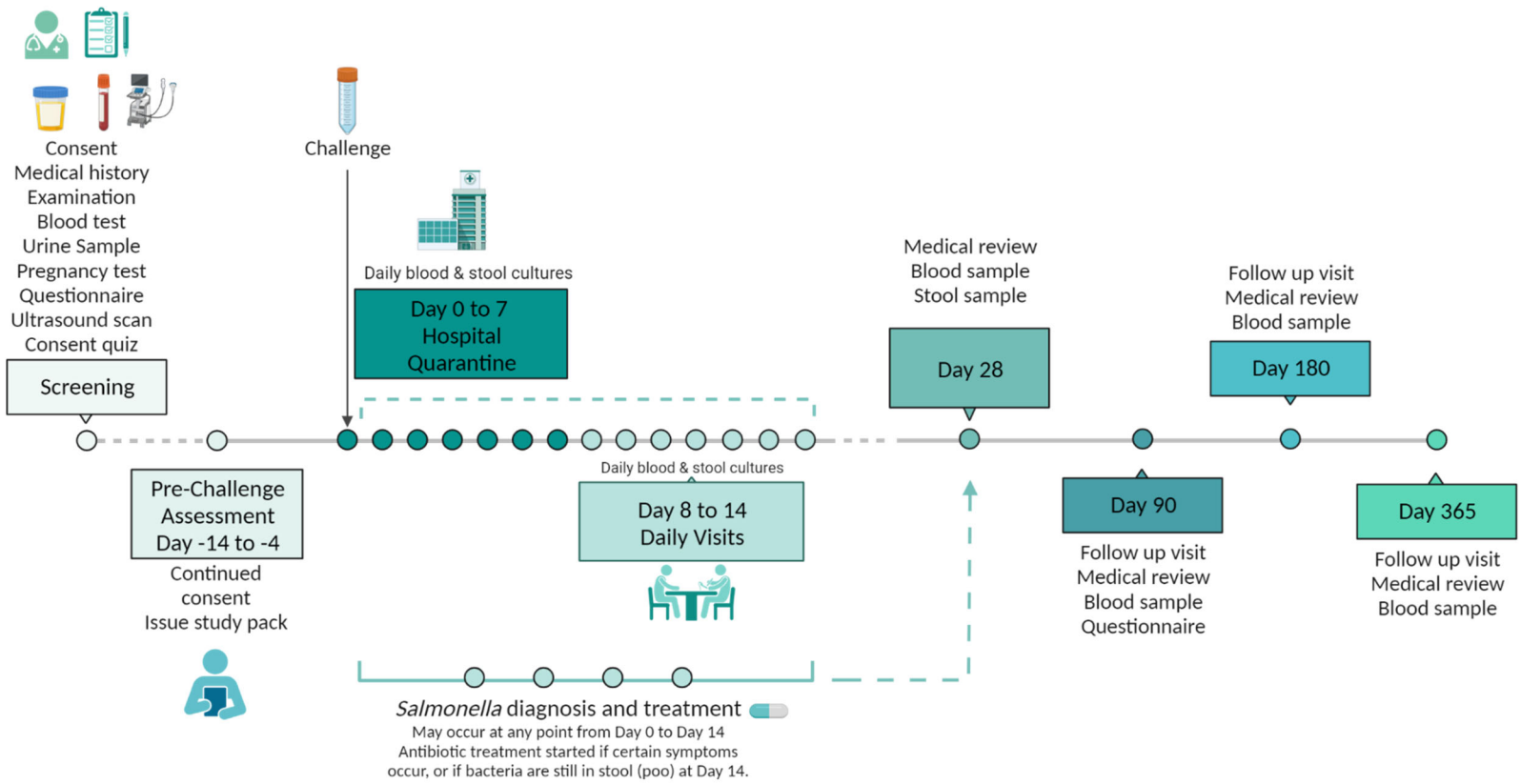


Figure 1 - Study overview. The quarantine period is expected to last 7 days. In some circumstances (i.e. if there are ongoing symptoms of diarrhoea after 7 days), participants may be asked to remain in quarantine until these symptoms have resolved. In rare circumstances, participants can be released from quarantine before day 7 – please see text below for details.

TABLE OF CONTENTS

MAIN SECTIONS

TOPICS

BACKGROUND TO THE STUDY

Why have I been invited?

We are inviting you to take part because you have expressed an interest in this study. Before participating, we need to make sure that you fully understand what the study involves and to understand the benefits and risks. We also need to make sure that you are healthy and unlikely to get severely ill from the infection. You will need to agree to the study requirements if you decide to take part.

We must make sure you have read and understand this participant information sheet before you decide to take part. If you have any questions or concerns, please ask a member of the study staff and discuss any of this information with your family, friends, or your doctor.

Do I have to take part?

No**.** Taking part in research is entirely voluntary. It is up to you to decide.

If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to change your mind or withdraw at any time, without giving a reason and without affecting the standard of care you receive. You will be reimbursed for any time you have spent in the study.

What are you studying?

We are a studying a family of bacteria called *Salmonella*.

There are over 2000 different types of *Salmonella,* each of which are subtly different.

The specific species of bacteria we are studying is called ***Salmonella* Typhimurium**. This belongs to a group of *Salmonella* bacteria that we call **non-typhoidal *Salmonella*** – or **NTS** for short.

What type of illness does *Salmonella* (NTS) cause?

In most people, *Salmonella* (NTS) will cause a gut infection, called gastroenteritis. The usual symptoms are diarrhoea, stomach-ache, and fever, which gets better after a few days.

In some vulnerable people, the infection can be more severe. It can get inside the bloodstream or parts of the body outside the gut. We call this more severe form of the disease "invasive NTS" (or **iNTS** for short). This more severe form almost exclusively occurs in people who have a poorly functioning immune system (for example caused by advanced HIV infection), or those who are very young, very old, or with specific risk factors like malaria or sickle cell disease.

How is it spread?

It is usually spread by eating contaminated food or drinking contaminated water. Sometimes, people can spread the infection to one another if hygiene measures – like handwashing – aren't followed.

Why are we studying *Salmonella*?

Invasive *Salmonella* (iNTS) is a very big problem globally, but especially in sub-Saharan Africa. We think it affects over half a million people every year. It mostly affects very young children (aged under 5), most of whom are malnourished or also have other illnesses, like malaria, sickle cell disease or HIV. We are interested in finding ways to prevent this infection, such as vaccines.

Are there vaccines against *Salmonella* (NTS)?

Not really. We currently have some vaccines against typhoid fever, which is a different illness caused by a specific type of *Salmonella* bacteria. However, we don't have any vaccines against the group of *Salmonella* (NTS) that we're studying.

Some groups are testing candidate *Salmonella* (NTS) vaccines in early-stage trials. These vaccines look promising, but more research is needed.

Our group is studying *Salmonella* (NTS) because in the future we want to help test new vaccines to prevent this illness. We plan to do this by developing a special type of clinical study called a **human challenge study**.

What is a human challenge study?

A human challenge study is a carefully managed medical research study, during which participants are intentionally given an infection in a safe way with healthcare support. These studies are done to understand diseases and find new ways to prevent and treat them.
You can read more about human challenge studies here **(https://www.hic-vac.org/public-information/human-infection-studies).**

Why are you developing a human challenge model for *Salmonella* (NTS) infection?

We know that these types of studies have been extremely useful to develop new vaccines for similar gut infections, like typhoid fever or cholera. In the future we plan to use a human challenge model to test new *Salmonella* vaccines. Having *Salmonella* vaccines that protect against severe disease could help save thousands of lives each year, especially of children living in sub-Saharan Africa where the disease is widespread.

Before we can do that, we need to make sure the model is safe and works as we expect it will.

What is the purpose of this study?

This is the first time that anyone has developed a human challenge model for *Salmonella* (NTS) infection. First and foremost, we need to make sure that the model is safe. Before we use the human challenge model to test vaccines, we need to better understand some technical details. Some of the specific questions we are asking (amongst other things) are:

- How many bacteria do we need to use to cause infection?
- What is the best strain of *Salmonella* (NTS) to use? Do different strains cause different symptoms?

- Does infection with *Salmonella* (NTS) give you protection and/or immunity against future infection?

WHAT DOES THE STUDY INVOLVE?

We will be undertaking a 'challenge' with one of two strains of *Salmonella* (NTS) bacteria (*Salmonella* Typhimurium). You will be asked to swallow a drink containing live *Salmonella* (NTS) under medical supervision. After this, we will closely monitor you for two weeks.

The first week will involve staying in hospital. We expect we will be able to discharge you after 7 days. If you still have symptoms of diarrhoea after 7 days, we may ask you to stay a bit longer until your symptoms of diarrhoea have settled.[1] **This may involve staying additional nights in the quarantine unit**.

In some rare circumstances, you may be released from quarantine **earlier** than 7 days, if it safe to do so. This will happen if 1) you have been diagnosed with *Salmonella* very early on in quarantine, 2) at least 4 days have passed since starting antibiotic treatment, 3) you have no ongoing diarrhoea and 4) the study team consider it safe for you to be discharged.

The next seven days after discharge, you come to the clinic daily. We will offer you treatment with antibiotics when you show symptoms of infection, like diarrhoea or fever or if after 14 days we can still detect *Salmonella* (NTS) in your stool (poo)).

We will use **two strains** of the *Salmonella* Typhimurium bacteria. Half of the participants in this study will be challenged with a strain of *Salmonella* that is common in the UK and half with a strain that originated in Malawi. There is some data from the lab which suggests that these bacteria behave differently, but we don't yet know the significance of this in healthy people.

This study is called a "dose escalation" study. This means that we start the challenge with a low dose of bacteria and gradually increase (or decrease) until about 60% to 75% of people exposed to the bacteria develop symptoms of *Salmonella* (NTS) infection.

In addition, we will be able to study how the immune system responds to the different strains of *Salmonella* (NTS), to understand how it prevents *Salmonella* (NTS) disease. This will add to our general understanding of the bacteria and could aid vaccine development.

Will I know which strain I will be challenged with?

You would be randomly separated into two groups to be challenged with either the 4/74 **UK strain**[2] OR the D23580 **Malawi strain**[3]. This means a computer programme would randomly assign you to receive either challenge strain. This is like 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.

---

[1] You need to be free of diarrhoea for 48 hours until you can be discharged from quarantine. This will be reviewed on an hourly basis, and you will be discharged from quarantine as soon as it is safe to do so.
[2] The specific name for this strain of Salmonella Typhimurium is 4/74, which belongs to the ST19 lineage.
[3] The specific name for this strain of Salmonella Typhimurium is D23580, which belongs to the ST313 lineage.

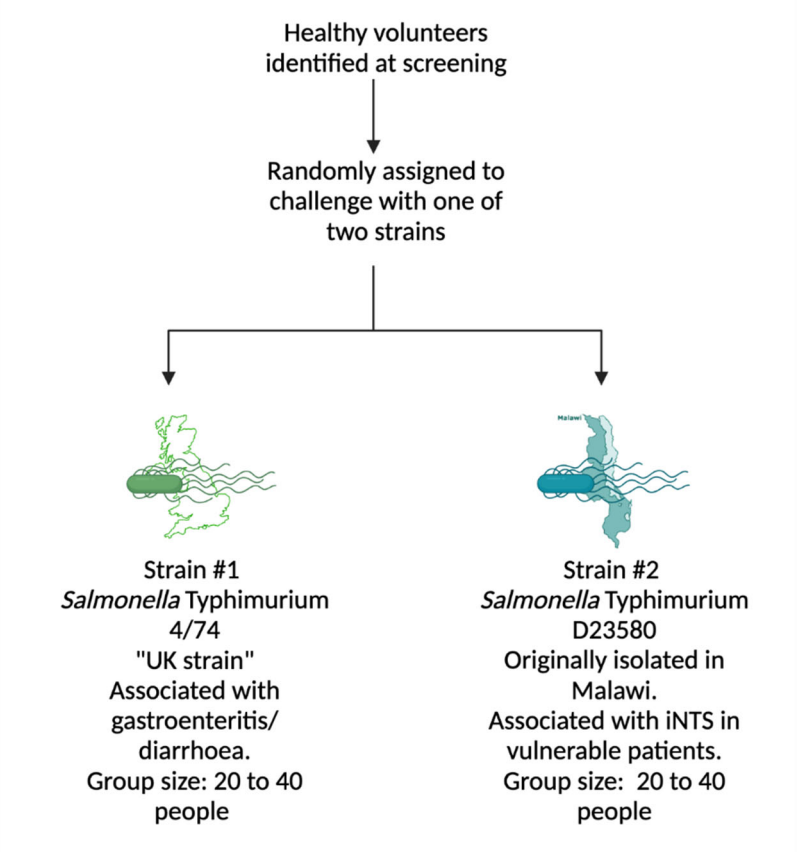


Figure 2 - Group allocation

GENERAL INFORMATION ABOUT THE STUDY

What will happen after you have identified the correct dose?

Once we have established the correct dose, we plan to use this in future studies to test vaccines.

How many people are there in the study?

We aim to enrol approximately **80** participants into this study. The exact number may be more or less, depending on the outcome of the dose escalation protocol.

What assurance can you provide that you can safely run the study?

Although we have not challenged volunteers with this type of *Salmonella* before, we do have lot of experience of performing challenge studies for related bacterial infections (like typhoid fever) and for other diseases (influenza, COVID-19). We will start with a low dose and only increase if it is safe to do so. The design of the study has been reviewed by independent experts and the sponsor (Imperial College London) to make sure it's as safe as possible.

Who can take part?

We are looking to recruit healthy adults aged between 18 and 50. Anyone taking part in the study needs to understand what the study will involve and be willing to follow the study rules. To take part in the study we must make sure that you are as healthy as possible and don't have any medical conditions that would put you at extra risk. You would need to have received at least two doses of COVID-19 vaccine.

How long the will the study last?

From start to finish, the study lasts for 1 year. There will be a busy phase at the start of the study where we will see you every day for around two weeks. For the first seven of these days, you will need to stay overnight in hospital. This might be a few days longer if you still have diarrhoea at the end of these 7 days. For the next seven days after discharge from the hospital, you will need to visit the clinic daily. If you develop *Salmonella* (NTS) infection you may need to attend an additional 5 visits. After this period, there will be four follow up visits.

The total number of visits depends on the outcome after challenge. You may have more visits, depending on whether you develop *Salmonella* (NTS) infection and on what day this happens. In total you will need to visit the clinic for up to 21 days if you do not develop *Salmonella* (NTS) infection. If you develop *Salmonella* (NTS) infection, you will need to visit the clinic for up to 26 days.

How long will each visit last?

Aside from the days when you will be staying in hospital, most of the other visits will last about 30 minutes. The very first visit – called the screening visit – lasts a little longer (about 90 minutes).

What will happen at these visits?

We will explain in more detail below. At most of these visits you will speak to a study doctor or a study nurse, who will ask you some general questions about your health. We will take some simple measurements like your pulse and blood pressure. At most of these visits we will need to take a blood test and we will also ask you to collect stool sample (poo).

What are the main risks of taking part?

The main risks of taking part are:

- developing gastroenteritis (including diarrhoea, stomach-ache, fever and vomiting),
- developing a more serious infection outside the gut (for example a blood infection),
- experiencing side effects from the antibiotics,
- developing post-infection complications including (but not limited to)
    - irritable bowel syndrome
    - reactive arthritis,
- passing the infection on to close contacts.

We describe all these risks fully, and the likelihood of them occurring, on pages 25-30 in this booklet. Please read this section carefully before you decide whether to take part. A study doctor will be available at the screening visit to answer any questions that you may have.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

In this section we will explain what taking part in the study involves, from first registering your interest, through to finishing the study.

This diagram illustrates the schedule of visits.

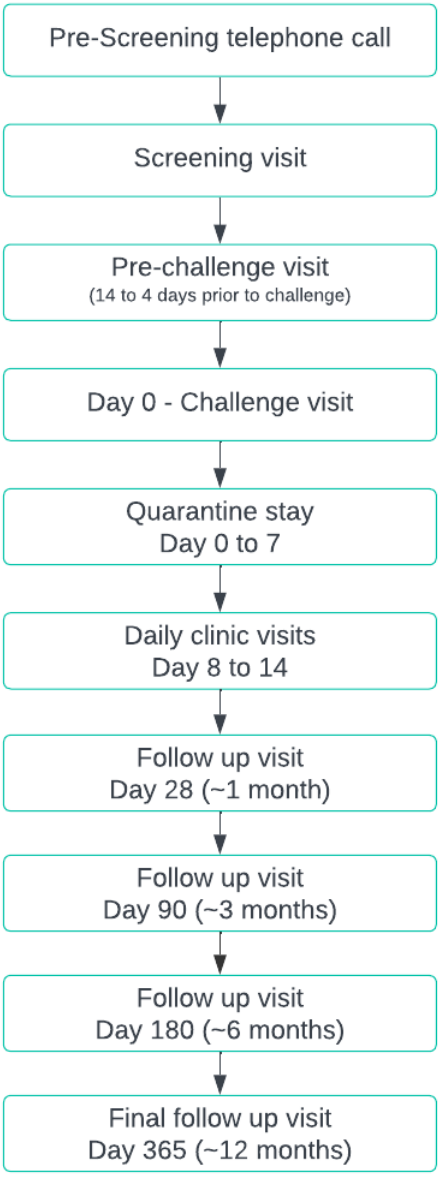


Figure 3 - Study schedule

Pre-screening

The first step is called pre-screening.

You will need to register your interest by contacting the study team (chants@imperial.ac.uk) or by visiting the website (www.imperial.ac.uk/infectious-disease/research/human-challenge/chants).
You will need to complete an online pre-screening questionnaire and submit your contact details. The study team will then contact you by telephone or email to discuss the study in detail. We will ask you some further questions relating to your eligibility for the study and answer any questions you may have.

Following the pre-screening telephone call, you may then be invited for a screening visit in person if you meet the basic eligibility criteria.

What happens at the screening visit?

This is an opportunity for you to learn more about the study, for you to ask any questions and for us to assess if you can take part. Please make sure you have read this booklet in detail before the screening visit.

To begin with, one of our study doctors will talk you through the ins-and-outs of the study in detail. We know there is a lot of information to absorb in this booklet, so we welcome questions to clarify any areas of uncertainty.

If, after this discussion, you are still interested in participating, we will ask you to sign a consent form. After this, we will need to undertake some assessments to see if you are eligible to take part.

What assessments do you do at the screening visit?

The screening tests are deliberately quite detailed. This is designed to make sure that you are suitable to take part in the study.

We start off by asking you some questions about yourself. We will spend some time asking about your medical history, to find out if you have any current or past health problems, or if you take any regular medicines. We will also need to ask questions about your background and home circumstances, like when and where you were born, what you do for work and who you live with. This is important to make sure there is no risk to any of your contacts or wider community if you were to take part in the study.

After this, we will perform a medical examination, where we will listen to your heart and lungs, examine your abdomen, check your blood pressure and so on. This is all designed to make sure you are healthy enough to take part in the study.

After this, we move onto performing some tests. This will include blood tests to check your blood counts (like your haemoglobin level, white blood cell count), kidney tests, liver tests, infection markers and an assessment of how well your blood clots. We test everyone for some important viruses, including hepatitis B/C and HIV. Other screening tests will include:

- An electrocardiogram or ECG (electrical tracing of the heart)
- A pregnancy test for women
- A urine sample to check for infection or kidney disease

- An ultrasound scan of the abdomen to check for gallstones (which puts people at higher risk of developing a long-term Salmonella (NTS) infection) – note that this may happen on another day and at Charing Cross Hospital (Fulham Palace Road, W6 8RF). You will need to fast (not eat or drink anything except water) for 6 hours before having the scan, so we will give you instructions closer to the time.

A detailed list of all the tests can be found in the **Appendix**.

We know that taking part in a study like this can be quite psychologically challenging, so we will also give you a questionnaire to assess your mental health at the time of screening.

Finally, we would contact your GP to gather more information on your medical history. We would need you to sign a form to say that you are happy for your GP to release this information. Your GP might send us information about your medical history that means you cannot take part in the study. If this happens, we will discuss the reasons for exclusion with you and attempt to answer any questions that you may have.

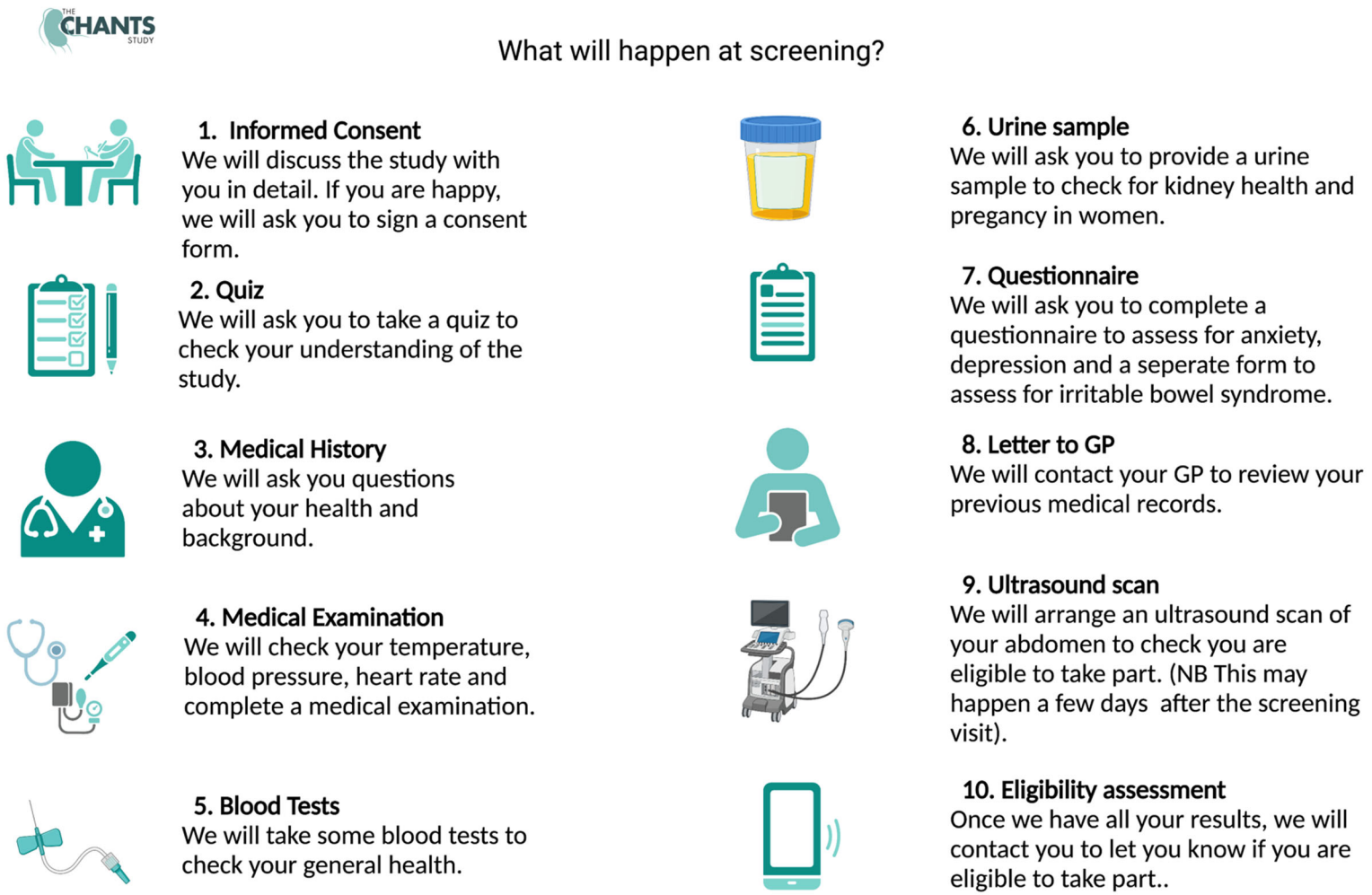
During your screening you would be asked to provide your National Insurance number (or passport number, if you do not have a National Insurance number). This would be entered on to a secure national database which helps prevent volunteers from taking part in too many clinical trials. The Trial Over-volunteering Prevention Service (TOPS) database is designed to ensure the safety of all our participants. As such, 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/.

Attending screening does not guarantee you will be enrolled in the study (there is a possibility that you may not be eligible for this particular study or that the study is full) but we will reimburse you for the screening visit.

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 decide there and then.

Figure 4 - Screening assessments



What happens after the screening visit?

After the screening visit, some people may decide they no longer wish to participate. Alternatively, we may identify something at the screening visit which means that you can't take part. Either way, if you are not eligible to participate, we will send you a letter thanking you for your time and explaining why you were not eligible. You will be reimbursed for the time you have spent at the screening visit.

If all the screening tests are satisfactory, you may still be eligible for the study. We will then invite you to a pre-challenge assessment.

What happens at the pre-challenge assessment?

The pre-challenge visit marks the start of your formal enrolment in the study. This will take place between a fortnight and four days (i.e. 4-14 days) before the challenge visit. Please remember that you are free to change your mind and withdraw from the study at any point.

At this visit, we will ask you to sign a second consent form to confirm that you are still willing to take part. We will ask you some questions to check that there have been no changes to your health since the screening visit. We will also perform a brief medical examination and collect some extra tests, including a second blood, urine, and stool (poo) sample.

We would get you set up with a diary that you fill in for 21 days after the challenge, recording your temperature, stools (poo), and any symptoms you may have. We will also ask you to record what you eat for breakfast, lunch, and dinner.

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

This visit will take place at the quarantine facility assigned to you by the study team (either at the Hammersmith Hospital, Charing Cross Hospital or Chelsea and Westminster Hospital), so we will show you where you will be staying and talk you through what to expect. About a week after this visit, we will plan to perform the challenge, if you are still willing to take part.

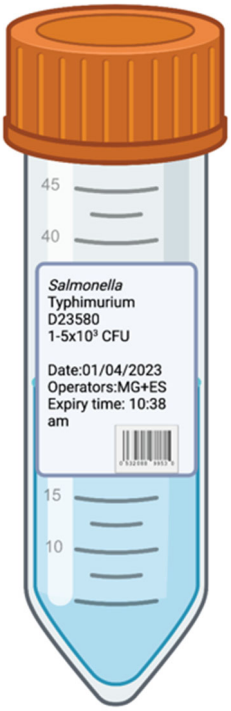
What happens at the challenge visit?

The challenge visit marks the start of the busy study period.

The challenge starts by admitting you to one of our dedicated facilities at either Hammersmith Hospital, Charing Cross Hospital or Chelsea and Westminster hospital. 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 take a urine pregnancy test. We will also perform a lateral flow test for COVID-19.

You would be asked to fast for 90 minutes before drinking the challenge agent. We would give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella*). This will be followed by a drink containing one of the two *Salmonella* (NTS) strains. The drink will be clear and tasteless, and the same volume as around two tablespoons. You would then be asked to fast for a further 90 minutes.

Figure 5 - Illustration of the challenge agent. It is given as a clear, colourless liquid. Volume 30ml (around 2 tablespoons).



We would then admit you to your room, where you will be checked on regularly by the study team. We will collect a blood sample at approximately 12 hours after the challenge. We would check that you have filled in a diary reporting your symptoms and your temperature. We would ask you to carry on filling out your diary twice a day for the following three weeks.

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

We will ask you to bring 2 stool (poo) samples[4] on the morning of the challenge (we will provide you with the necessary kit).

What happens after the challenge? (Day 0 to Day 7 –quarantine stay in hospital)

You would be admitted to a quarantine unit in hospital for at least 7 days and would be reviewed regularly throughout the day, every day.

After the challenge you may or may not develop symptoms of *Salmonella* (NTS) infection.

In the morning, we would first check that you are still willing to participate in the study. We would then review your symptoms, measure your temperature, pulse and blood pressure. After this, we will take a blood sample every day. This blood sample would be tested for the *Salmonella* (NTS) bacteria

[4] This needs to be collected within 24 hours of the appointment and can be stored in a fridge after collection. We will provide you with the necessary kit to collect the sample and pots/bags to store it.

and to study your body's immune response to the infection. Blood tests will also be taken for genetic analysis to see whether a particular genetic makeup can protect against infection and affect your response to the challenge.

Throughout the day, we will ask you to record every time you have a bowel movement. The study staff will help you to fill out a chart (called a stool chart), that details how many times you have had a bowel movement, the volume passed and whether you have had diarrhoea.

Over the course of each day, a member of the study team will come to visit you at regular intervals to check if there is anything you need and to check your temperature, pulse, blood pressure and your stool chart. We will ask everyone to update the study team if they develop any new or changing symptoms, so that we can offer you the best treatment.

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 *Salmonella* (NTS) infection.

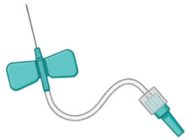
What happens after the challenge? (Day 0 to Day 7 –quarantine stay in hospital)

Medical Review
We will ask you questions about your health and how you are feeling

Other samples
On some days we will collect other samples, like saliva.

Examination
We will check your temperature, blood pressure, heart rate and take other measurements

Diary
We will ask you to record any symptoms using a diary card



Blood Test
We will take a blood test each day to check your health and to test for *Salmonella* infection

Stool chart
We will ask you to record when you have any bowel motions.

Stool sample
We will ask you to collect a stool (poo) sample when you have any bowel motions to test for *Salmonella* infection

Monitoring for treatment
We will monitor you closely to see if we need to start treatment

Figure 6 - Inpatient quarantine

Why do I need to be admitted to hospital and what will quarantine be like?

We will admit everyone to hospital for at least 7 days. This is because we want to monitor you closely, to make sure that you don't develop a more severe infection and so we can start treatments (like antibiotics) as soon as possible. We also want to make sure that there is minimal risk of passing on the infection to people outside the study.

You will have your own room and en-suite facilities. There will be TV and Wi-Fi, and you can bring your own personal devices (laptop, mobile phone, games console) so that you can work, study, keep in touch with friends and family, and entertain yourself during quarantine. You may also bring small items for exercise (for example a yoga mat). We will provide you with antimicrobial wipes and spray to clean any personal items before leaving quarantine.

Will I be allowed visitors?

Access for visitors will be limited, to minimise the risk of transmission. A limited number of visitors would be allowed if you are not considered infectious. This is usually if you do not have diarrhoea for 48 hours. Any visitors you have would need to agree to certain restrictions and follow a detailed hygiene protocol.

Can I mix with other volunteers?

We ask that you avoid mixing with other volunteers to prevent transmission between people.

Will I be provided with food?

You would be provided with food during your stay in the hospital, but feel free to bring in your own food (such as snacks) in addition. We can cater for vegetarian, vegan and other dietary requirements; please let us know before admission if you have any needs or allergies/intolerances. You will be allowed to bring snacks and order external meals. We will ask you to record details of your diet in the diary card.

What happens after the quarantine period? (Day 8 to 14)

We expect most participants will be released from quarantine after 7 days, but we may ask you to stay longer if you still have symptoms. After this, we would still need to see you every day for another 7 days in the clinic. You will need to remain contactable (by mobile phone or email) for at least another seven days, up until we have confirmed clearance of *Salmonella*.[5] This is an important safety requirement, as we may have to update you of any changes to your blood tests or inform you of any changes to your appointments.

At these follow up visits we would review your symptoms as recorded in your diary, measure your temperature, pulse, and blood pressure, and take a blood sample. You will be issued with a thermometer to record your temperature twice a day in a diary card. These samples would be examined for the *Salmonella* (NTS) bacteria and to study your body's immune response to *Salmonella* (NTS) infection. We would ask you to bring 2 fresh stool (poo) samples to each visit.

[5] Because of the schedule of study visits, we recommend that you are easily contactable by mobile phone or email for the entire duration of the study, but this is particularly important in the first 6 weeks after challenge.

In the unlikely event that you were to develop severe symptoms after you have been discharged from hospital quarantine, we may ask you to return to hospital for observation and/or further treatment.

What happens if I get *Salmonella* (NTS) symptoms?

You could develop symptoms of *Salmonella* (NTS) at any point after challenge. We might expect symptoms to start as soon as 12-48 hours after challenge, but this can range from as short as 4 hours to as long as 3 days. Whilst everyone is different, we would expect symptoms to last between 3 and 7 days on average.

In healthy, young people *Salmonella* (NTS) infection is usually short lasting and gets better by itself, often without any treatment.

The usual symptoms are:

- Diarrhoea
- Stomach ache
- Fever
- Vomiting
- Loss of appetite

Some people may report a headache, may feel tired and generally unwell, with muscle or joint aches.

If you develop *Salmonella* (NTS) infection we will start antibiotic treatment, which will shorten how long the symptoms will last. Once you have started the course of antibiotics, we will offer you other medicines, such as paracetamol to lower your temperature or anti-sickness tablets to control any other symptoms you might have. If needed, we will also provide you with rehydration fluids to drink or fluids through a drip.

Could I develop more severe symptoms?

Healthy people given early antibiotic treatment do not usually 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.

There is a very small risk of a more serious form of *Salmonella* (NTS) infection or other complications. The risks of this are discussed in more detail below.

Can I give *Salmonella* (NTS) to anyone else?

The risk of passing on *Salmonella* (NTS) to someone else is very low, provided that you strictly follow the hygiene measure we have put in place. The risks of transmitting to other people and the hygiene measures are detailed below.

We do ask that you inform people who live in your house or other close contacts (e.g. your partner) if you do take part. We can give you an information sheet to pass onto them upon request. To offer peace of mind, we can also offer them a screening test to check that they are not infected with *Salmonella* (NTS) if you or they are worried.

Public Health notifications

Whenever anyone is infected with *Salmonella*, we have a legal obligation to notify the local public health authorities. The purpose of this is to allow them to track any episodes of *Salmonella* in the community.

In practice, we pass on your name, address, and telephone number, as well as the date and time of your challenge to the local health protection unit. There is nothing that you need to do other than follow the hygiene measures described below.

We will inform the public health authorities when you have been started on antibiotics and when we have confirmed that you are clear of *Salmonella* infection. If you are contacted by a member of the public health authority, please ask them to contact the study team by telephone (07894986332) or via email (chants@imperial.ac.uk).

Will I be treated with antibiotics?

In general, all participants with a detectable *Salmonella* (NTS) infection will be offered antibiotics. The timing of treatment may differ depending on your symptoms and the results of your tests.

In some circumstances, the side effects of antibiotics may outweigh any potential benefit. For example, you may progress through challenge with no significant symptoms and your stool (poo) tests negative for *Salmonella* on several consecutive days. In this circumstance, we will discuss different options including whether antibiotics are likely to offer benefit and why. You may still be offered antibiotics if treatment is felt to be needed for your safety or if you feel strongly that you would like to be treated.

When will I be treated with antibiotics?

We will start antibiotics as soon as you meet the criteria for treatment. This might be if:

- You have a persistent high temperature (≥38°C) lasting for at least 12 hours,
- You have a positive blood test for *Salmonella* (NTS)
- You have significant diarrhoea.
- You have significant other symptoms that may benefit from antibiotics.
- The study doctors judge that antibiotic treatment is needed for your own safety.

Some people may not develop any symptoms after challenge. In this case, we may still offer you a course of antibiotics two weeks or more after challenge if the bacteria are detected in your stool (poo).

If we can still detect bacteria in your stool (poo) following antibiotic treatment, we may offer you a short course of a second different antibiotic to clear it up and re-test your stool samples.

Which antibiotics will I be offered?

We would use either an antibiotic called azithromycin, or one called ciprofloxacin depending on your symptoms and test results. Both come as a tablet, taken either once or twice a day. They are recognised as being the best treatments for *Salmonella* (NTS) infection and are widely used for treatment of many different types of infections. In most people, the treatment lasts for 5 days. If you

have a positive blood test (blood culture) for *Salmonella* (NTS), we will treat you for a slightly longer period (10-14 days). We may need to use another antibiotic, called ceftriaxone, if we need to change your treatment for whatever reason.

What are the potential side effects from the antibiotics?

Most people do not have any side effects from antibiotics. Occasionally the antibiotics can cause diarrhoea or stomach upset. The potential side effects of antibiotics are detailed below.

Will I be followed up with afterwards?

Follow up would then be at 1, 3, 6 and 12 months after the 'challenge' day. You are free to contact the study team at any time in between the scheduled visits and, if needed, we can schedule an *ad hoc* appointment (we will contact you to add, change or confirm appointments by email or mobile phone).

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 (poo) samples would also be taken on most of your study visits, 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 infection or not. A maximum of 708ml (about one pint) of blood will be taken over the 1-year 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, you 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 *Salmonella* (NTS) bacteria and vice-versa. To study this, we will collect samples of stool and saliva as at certain points during the study.

What would happen to any samples I give?

The blood, saliva, and stool samples collected during this study would be analysed in the Imperial College Healthcare NHS trust laboratories and Imperial College London 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. The details regarding privacy and data storage are described at the end of this information booklet.

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 before we have treated you, study staff would make every effort to ascertain your whereabouts (e.g. going to your home).

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

Will you be looking at my genes?

Blood samples contain genetic information in the form of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA contains the genetic 'instructions' for the ways the various parts of your body work. This information can also be obtained from a process called 'sequencing' of your RNA.

Differences in these genetic 'instructions' between individuals may help to explain why some people are more likely to get a particular disease, why some people become sicker than others, and why some medications work better for certain people. We would like to study your genetic information in the blood samples that will be collected from you during the study to improve its knowledge of how the *Salmonella* (NTS) bacteria affects the human body in the disease process. As medical and scientific knowledge develops, samples we collect now could be invaluable to future research.

Some of the blood samples we collect can be used to look at your genes. The genes we will be looking at are those which are involved in protecting us from infections. This will involve looking at genes that are turned on and off during infection with *Salmonella* (NTS) and whether the patterns of these are linked to the likelihood of developing symptoms. In addition, we may look at your DNA sequence directly to see if there are inherited differences that influence risk of infection.

Please note that your genetic information will not be used for your medical care. The test results cannot be used to make a diagnosis of your health, and neither you nor the study doctor will be given specific information about the results. If you do not want us to perform genetic testing, you can still take part in this study, but we will not perform these tests.

If you agree to let us perform genetic testing, you will be asked to sign an optional statement on the consent form.

Do I have to have genetic testing of my samples?

No, you do not have to. Agreeing to the genetic testing of your samples is completely optional and if you do not consent to genetic testing of your samples, you will still be able to continue in the study. Your decision will not affect the care that you will get from the study doctor.

If you do consent to genetic testing, you can change your mind at any time and withdraw your consent. This will not affect the compensation you are entitled to receive as a result of taking part in the study.

If you wish to withdraw your consent, please notify the study doctor. If you withdraw your consent to genetic testing of your samples, genetic testing will not be done. A record of your signed consent and your withdrawal would be kept as evidence of your wishes.

What if any of my test results were abnormal?

If abnormal results or undiagnosed conditions are found during 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.

Future mortgages, travel insurance, private healthcare or life insurance may be affected if a previously unrecognised problem is found during screening or during the study.

Is there any risk if I were to get pregnant?

Salmonella (NTS) 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 (this will be discussed with you at the screening appointment, including extra precautions during antibiotic treatment) until tests show that the *Salmonella* (NTS) bacteria had been fully treated. A pregnancy test would be carried out at the screening visit before the challenge and prior to starting antibiotics.

Contact with young children, pregnant women 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), pregnant women or with anyone who has a problem with their immune system until we were sure that you did not have the *Salmonella* (NTS) bacteria in your body (at least six weeks after challenge).

Food handlers

Salmonella (NTS) can be transmitted in food handled by people who are infected with the bacteria and shed it in their stool. 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 health or social care, you will have to agree to stay away from your work or studies until we were sure that you did not have the *Salmonella* (NTS) bacteria in your body (you have completed the antibiotics and provided 3 consecutive negative stool samples that are obtained at least 48 hours apart). We would need to inform your employer (or occupational health department) of your participation in the study. The same would apply if your work entails having direct contact with people or patients who are susceptible to *Salmonella* (NTS) infection (including those under 2 years of age) or in whom *Salmonella* (NTS) infection would have particularly serious consequences.

What are the risks of taking part in the study?

In this section, we will go through the potential risk of taking part in this study. We have designed the study in such a way as to minimise the risk. The risk of taking part in this study is low but – as we are deliberately infecting healthy volunteers – this risk is not zero. It is very important that we explain in as much detail what the potential risks are, so that you can make an informed decision.

In this study, we anticipate that most volunteers will develop symptoms of *Salmonella* (NTS) infection. Some individuals in the study will remain well and experience no symptoms.
We have classified the probability of experiencing the risks as follows:

- Uncommon: 0.1%-1%
- Common: 1%-10%
- Very common ≥10%

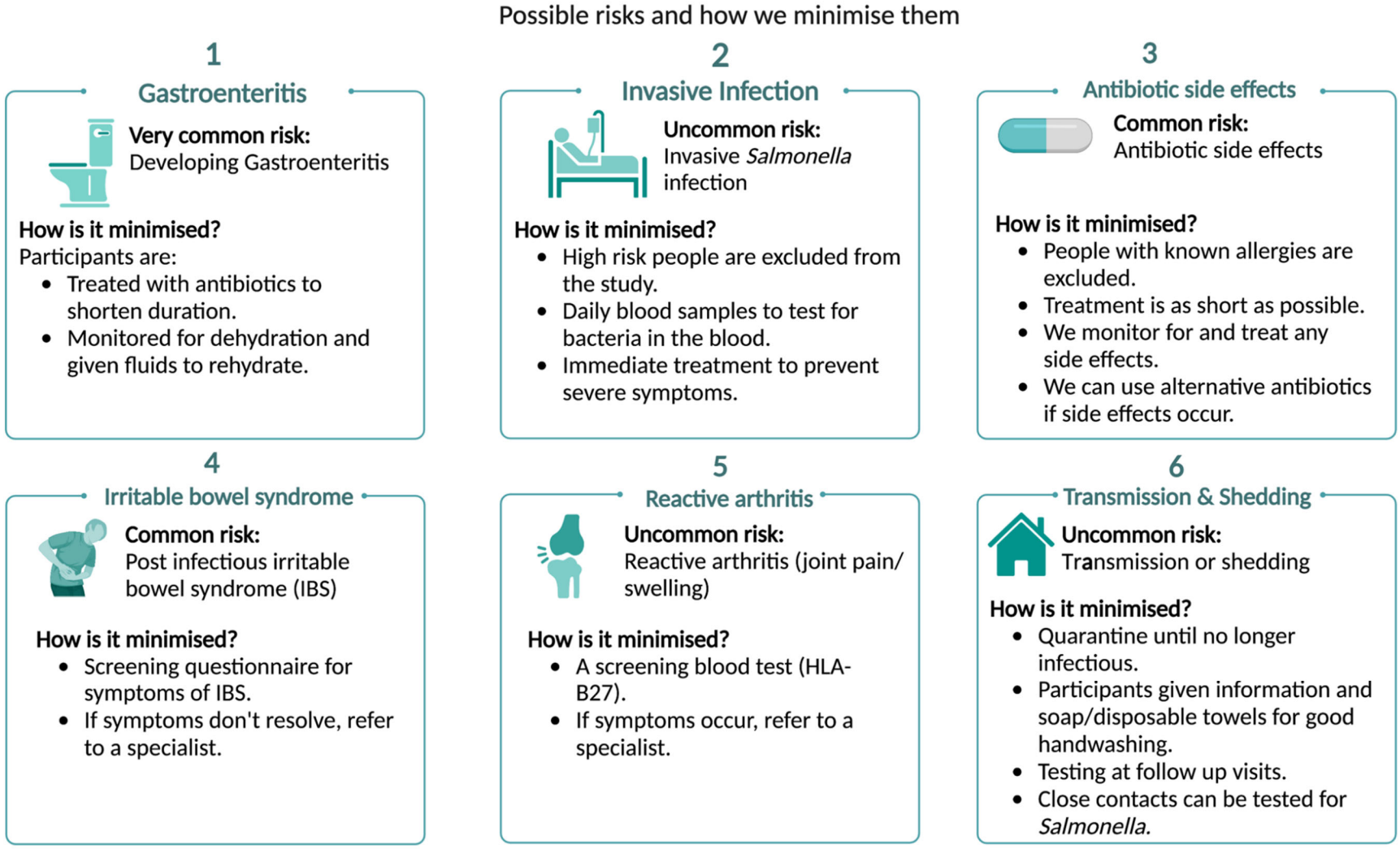


Figure 7 - Possible risks and how we minimise them.

The risk of *Salmonella* (NTS) gastroenteritis

Expected frequency: Very Common

The most likely risk is to develop gastroenteritis. This usually presents with any of the following symptoms:

- Diarrhoea
- Stomach ache
- Fever
- Vomiting
- Loss of appetite

Some people may report a headache, may feel tired and generally unwell, with muscle or joint aches. Some people may notice blood in their stool (poo).

The biggest risk of *Salmonella* (NTS) gastroenteritis is dehydration.

The time from exposure to developing symptoms is about 12-48 hours but can range from 4 hours to 3 days. Overall symptoms usually last 4 to 7 days.

What will you do to minimise the risk?

During the time we expect you to develop diarrhoea, you will be closely monitored in the quarantine unit.

In healthy young people, *Salmonella* (NTS) gastroenteritis will usually get better by itself without any specific treatment.

We know that antibiotics normally help the symptoms get better faster, so we will treat all volunteers with antibiotics when they develop certain symptoms.

We will protect against dehydration by closely monitoring your heart rate and blood pressure, and measuring the number and volume of stools (poo) passed. We will provide you with plenty of fluids and guide you on how much (and how frequently) you should drink. If you are showing signs of dehydration, we can give you fluids into a vein via a drip.

The risk of invasive *Salmonella* (iNTS) infection

Expected Frequency: Uncommon

There is a very small risk of causing a more serious form of *Salmonella* infection, where the bacteria can enter the bloodstream – this is called **invasive NTS disease** (iNTS). This is different to gastroenteritis and would require early treatment with antibiotics.

If invasive infection is left untreated, this form of the disease can cause severe symptoms (like dangerously low blood pressure or 'sepsis') or infection elsewhere in the body (such as bones, joints or blood vessels) or even death.

What will you do to minimise the risk?

We do not anticipate this to happen in our volunteers, as this severe form of the disease nearly always affects highly vulnerable people, who would be excluded from participation in this study.

But for your safety, you will be closely monitored in the quarantine unit for at least 7 days after the challenge, and trained study staff will do regular assessments and take blood samples. To make sure

we are on the lookout for the severe form of *Salmonella* (NTS) infection, your daily blood samples will be tested for bacteria. So even if you do get a blood infection, it is highly unlikely to cause any serious symptoms such as sepsis because we will detect it early and start treatment immediately.

The risk of post infectious Irritable Bowel Syndrome (IBS)

Expected Frequency: Common

Some people develop "post infectious Irritable Bowel Syndrome (IBS)". This is thought to be because the infection (and/or the antibiotics used to treat the infection) can have an effect on the bacteria that normally live in your gut. It can cause changes to bowel habits (increased or reduced frequency of bowel movements), diarrhoea, stomach cramps and wind.

What will you do to minimise the risk?

You will be closely followed up for a year following challenge, where we will ask you specifically about these symptoms. We would ask you to complete a questionnaire at the start and end of the study. Anyone who has a previous history or irritable bowel syndrome would be excluded from the study.

Symptoms of post infectious IBS will almost always fully get better without treatment, but the recovery time can vary from weeks to months. If symptoms do not completely go away, we will contact your GP (with your permission) to arrange a referral to a specialist. Whilst we expect this to be a short-term effect, we will be collecting samples up to one year after the challenge to study the impact of *Salmonella* (NTS) infection on the normal gut bacteria.

The risk of reactive arthritis

Expected Frequency: Uncommon

There is also a small risk of developing joint pain or swelling after infection. This is called 'reactive arthritis'. If it occurs, symptoms will normally appear 1-4 weeks after infection and you might experience pain or swelling in joints or pain in the lower back. Most people who develop reactive arthritis find symptoms go after 6-12 months, but a small proportion of people may develop symptoms lasting over 12 months.

What will you do to minimise the risk?

This complication is thought to occur more frequently in people with a particular genetic marker (called HLA-B27), which we would screen you for prior to enrolling for the study.

If you develop symptoms suggestive of reactive arthritis, we will contact your GP (with your permission) to arrange a referral to a specialist for further investigation and management.

The risks of antibiotics

Expected Frequency: Common

The most common risks of antibiotics are side effects of nausea, vomiting, diarrhoea, loss of appetite and changes to sense of taste, headache, feeling tired or dizzy, or thrush.

A small number of volunteers could develop an intolerance or allergy to the antibiotics. This may cause an upset stomach, nausea, vomiting or other symptoms. An allergic reaction is unlikely, but may result in a rash, lip or tongue swelling, difficulty in breathing or, in very rare cases, anaphylaxis (a potentially life-threatening allergic reaction).

Very rarely, the antibiotics we use in this study can cause rash, heart rhythm abnormalities, mood disturbance, liver and kidney problems, headache, problems with the blood and sleepiness. The main antibiotic used in the study (ciprofloxacin) can very rarely cause tendon or joint problems.

Antibiotic treatment may increase the risk of carriage of drug resistant bacteria. This could make treatment of future infections more challenging.

The absorption of antibiotic tablets can sometimes be affected by antacids and iron supplements.

Lastly, antibiotics could interfere with the absorption of the oral contraceptive pill, making it less reliable.

What will you do to minimise the risk?

The antibiotics to be used in this study are usually well tolerated and only occasionally cause severe side effects. However, we have put lots of measures in place to minimise the risks.

- If you have a known allergy to antibiotics before starting, then you would not be able to take part.
- Antibiotic treatment duration will be as short as possible.
- If one antibiotic cause side effects, the treatment could be stopped early or switched to a different antibiotic.
- We will take blood tests, so that we can identify any side effects early.
- We ask that you continue to complete your diary after starting treatment to monitor for any side effects from the antibiotics.
- We ask that you avoid taking iron tablets and antacids whilst you are taking the antibiotics.
- If you take the oral contraceptive pill, we recommend that you use additional barrier contraception (such as condoms) whilst you are taking the antibiotics.
- You can contact a study doctor 24/7, who will be able to offer advice if you develop any problems with treatment.

The risk of transmission and shedding

Expected Frequency: Uncommon

Salmonella (NTS) infection is usually caused by eating contaminated or poorly prepared food. There is a very small risk of transmitting infection from person-to-person if good hygiene practices aren't followed, such as not thoroughly washing hands after using the toilet and before preparing food (particularly uncooked food – thorough cooking kills the bacteria).

A small percentage of people (<1%) who get a *Salmonella* (NTS) infection can go on to carry the bacteria and excrete the bacteria in their stools a year or more after challenge. These people are known as 'chronic carriers' and we know that this almost always happens in people with gallstones.

What will you do to minimise the risk?

It is very unlikely that anyone could contract *Salmonella* (NTS) infection from you if you maintain good hand washing and food preparation habits. Nevertheless, we have put lots of measures in place to minimise the risks.

- If you had close contacts who would be at high risk if they were to contract *Salmonella* (NTS), then you would not be able to take part in the study.

  - This includes young children, pregnant women, or people living in your house who have an impaired immune system.
- If your job might put the general public at risk, then you would not be able to take part in the study.
  - This includes jobs involving handling food or jobs in health and social care.
- We know that most people are at highest risk of passing on infection to other people when they have diarrhoea.
  - For that reason, we will need you to remain in the hospital quarantine for 7 days or until your diarrhoea has settled (whichever is longer).
- After leaving hospital, we would give you detailed advice on how to prevent transmitting infection to other people. We will give you antibacterial soap and towels to help keep good hand hygiene.
- To reassure your close contacts we would offer them information at the start of the study and a screening test to check that they are not infected with *Salmonella* (NTS) (after you have started antibiotics).
- We will ask you to bring in 3 stool samples after you have completed your antibiotics.
  - This will prove that the *Salmonella* (NTS) bacteria have been fully cleared.
- We know that gallstones are a risk for being a chronic *Salmonella* (NTS) carrier.
  - 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 disease specialist for further antibiotic treatment.

Long term shedding

Most people will have cleared the bacteria within a week or so after the challenge, but on some occasions the *Salmonella* bacteria can survive in the gut for longer without causing any symptoms. If we detect *Salmonella* bacteria in your stool during the first few weeks or months after challenge, we call this "convalescent shedding" – this is common. If we can still detect *Salmonella* at 1 year after challenge, we call this "chronic carriage" – as mentioned above, this is rare and usually linked to having gallstones.

Convalescent shedding is seen commonly in patients with *Salmonella* infection. If this were to occur, we may offer you a second short course of antibiotic treatment and collect further stool (poo) samples to check for clearance. If bacteria were still detected after a second course of antibiotics, we would not offer you any further courses, but we would continue to monitor you closely and refer you to an infectious disease specialist if it doesn't clear up fully by the end of the study.

If you experience this long-term shedding but have no diarrhoea, then you are not at high risk of passing the infection to other people. The public health guidelines in the UK suggest that you are infectious when you have diarrhoea and for 48hrs until after the diarrhoea has resolved. However, to be on the safe side we would ask you to do the following until you have provided three negative stool samples:

- Continue practising good hand hygiene (i.e. regular handwashing).
- Minimise close contact with young children, pregnant women, and people who have problems with their immune systems (including clinical and social care duties).
- Continue using effective contraception.
- Avoid commercial food preparation and handling.

Are there any other risks of being in the study?

- Infection with *Salmonella* (NTS) can sometimes cause other delayed symptoms after the initial infection has cleared. These are called "post infectious" complications. Generally, these may be due to an abnormal immune response to infection and could affect parts of the body other than the gut.
- You may become **anxious, lonely, or depressed** by being confined to the quarantine unit for the minimum of 7 days. The study team will try to provide comfort if this is the case, and you will be able to make phone and video calls with your friends and family. A small number of visitors will be allowed, but they would have to comply with a strict hygiene protocol.
- Your personal **private space will be limited**, and you will be visited frequently by study staff to check on you.
- Some of the tests or procedures in the study may be **stressful or make you worried** about how others might see you, such as concern about being tested for HIV.
- We will tell you as soon as possible if we become aware of **new information** that could change your mind about taking part in the study.
- If you have any **insurance policies**, you should check whether taking part in this research study affects them.
- If you receive **state benefits** you should check if the compensation received from taking part in this study affects payments to which you are entitled.
- You should carefully consider the risks involved in taking part in clinical research in the context of your career choices, as **long-lasting symptoms may affect your work**. If you do experience symptoms that impact your work, compensation arrangements are detailed below.
- Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint.

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 this disease, which could lead to the development of improved vaccines against *Salmonella* (NTS).

Reimbursement

You will receive up to **£3002** if you remain in the study for the entire period and attend all routine study visits.

You would be reimbursed for your time, travel and for inconvenience based on the following figures:

- Travel expenses: £15 per visit (total for up to 21 visits including screening and delivery of clearance samples = £270)
- Inconvenience of blood tests: £10 per blood donation (total for up to 21 blood tests, including screening = £210)
- Inconvenience of screening ultrasound scan: £50 (total for 1 scan = £50)
- Inconvenience of providing clearance stool samples: £10 per visit (total for three visits £30)
- Time off work compensation – calculated using the London living wage rate of £11.05 an

hour[6] - £2442.05

You may be asked to attend **extra** visits (up to 5) for the purposes of safety follow up. You will be reimbursed for any extra visits that you are asked to attend. For each extra visit, your reimbursement is calculated based on the following figures:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per blood donation
- Time off work compensation – calculated using the London living wage rate of £11.05 an hour for 2 hours.

If a participant needs to attend all extra 5 visits, the maximum additional reimbursement will be £235.50 (making the overall reimbursement **£3237**).

Payments will be made via internet bank transfer. You will be asked to provide banking details including account name, sort code and account number. All details will be stored confidentially and retained by Imperial College London while the participant is actively involved in the study.

Payments will be made after you have attended the following visits: Screening, 28 Days, 3 months, 6 months, and 1 year. 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.

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.

Medical photography and film

If you were to have any clearly visible signs of *Salmonella* (NTS) 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.

[6] An hourly rate will be paid depending on the duration of the visit and will include travel time to and from the clinic. The screening visit will be compensated for 4 hours. The pre-screening visit on Day -7 will be compensated for 3 hours. Visits on day 11, 12, 13, 14, 28, 90, 180, 365 and additional study visits will be compensated for 2 hours. The days in quarantine (Day 0 to 7) will be compensated for 18 hours. Days 8, 9 and 10 will also be compensated for 18 hours in case of the need for a prolonged admission.

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* (NTS) 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 *Salmonella* (NTS) 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 the local health protection unit. This follow up would include you providing stool samples, ensuring you are clear of *Salmonella* (NTS).

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.

LEGAL INFORMATION

In this section we outline important legal information relating to the study.

What if I want to withdraw from the study?

You are free to withdraw from the study at any time you wish. If you decide to withdraw your consent and `leave the study' during the quarantine phase, you will be very strongly encouraged to remain in the quarantine unit until you are no longer contagious. This is for both your safety and that of others whom you could infect as a contact. In this situation, we would continue to optionally offer you all procedures considered important for safety purposes by the study team but would stop any research procedures. This would include:

- Regular vital signs (heart rate, blood pressure, temperature etc.)
- Medical review of any symptoms
- Safety blood tests (but not research ones)
- Antibiotic treatment

By remaining in the unit, it would allow close follow-up by the study medical team and for us to monitor your treatment. If you have to leave the quarantine unit before you have been formally discharged, we will contact the local health protection team, who may wish to follow you up in the community.

If you decide to leave the unit early:

- You will be advised about hand-washing and other infection control measures
- You will need to be transported home in private transport
- With your agreement, you will be contacted daily by the study staff (i.e., study doctor or nurse) via phone call to check on your health and to remind you of any self-isolation requirements until the study doctors are satisfied that daily follow up can end.

If you withdraw from the study, any samples and data collected before your withdrawal will be used/stored unless you specifically request otherwise. However, if any of your anonymised data has been incorporated into the study, it will not be withdrawn or erased to comply with our legal obligations and to maintain the scientific integrity of the study.

What if something goes wrong?

You must tell the study staff immediately if you have any health problems during the study. You will be given an emergency contact card when you are discharged from quarantine, which provides a 24-hour telephone service in case you need to contact us outside of office hours. If you need to attend another doctor for health problems relating to the study, we will ask that doctor to provide details that will help us follow up your care and investigate the possible reasons for these health problems.

If you are injured or experience symptoms worse than the mild short-term symptoms listed above, we will offer you the appropriate treatment. If you suffer any significant worsening in health or well-being caused directly by participation in the study, your medical care will be provided by the National Health Service (NHS).

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Malick Gibani, chants@imperial.ac.uk). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team'.

Who is organising and funding the research?
This research is funded by the Wellcome Trust. The study is being sponsored by Imperial College London. The trial itself will be conducted at the Imperial Clinical Research Facility (located at Hammersmith Hospital), Charing Cross Hospital and the Chelsea and Westminster hospital NHS foundation trust.

Who has reviewed the study?
The study has been reviewed by the study sponsor (Imperial College London). It has been approved by an independent research ethics committee (London – Fulham Research Ethics Committee) and has also been approved by the NHS (Research & Development approval).

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. Imperial College London, 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.

In the event of a study participant experiencing a serious adverse event, permission may be sought from the participant to access medical records (e.g. discharge summaries or correspondence) from NHS services. Personal identifiable information will only be stored on password-protected computer servers at the study site. In the unlikely event that a participant becomes very unwell, they will be admitted to the Infectious Diseases Ward or other suitable wards at the participating hospital. Their care at this point will be under the admitting Consultant and their team and NHS medical records will be used. The study team will seek permission from the participant to access these medical records as needed.

By agreeing to take part in this study, you do not give up any legal rights to other treatments that may be available to you for an injury or illness caused by the study or study procedures. Imperial College London holds insurance which applies to this study. If you experience harm or injury as a direct result of taking part in this study, beyond the expected mild symptoms during the quarantine period, you will be eligible to claim compensation via Imperial College London's non-fault compensation scheme. The amount of compensation you receive will be assessed independently based on any harm or disability you suffer. This does not affect your legal right to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform Dr Malick Gibani (m.gibani@imperial.ac.uk). The normal National Health Service mechanisms (https://www.nhs.uk/using-the-nhs/about-the-nhs/how-to-complain-to-the-nhs/) are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Research Governance and Integrity Team (https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/)

Has the clinical study been registered?

A description of this study will be available on a clinical trials database e.g., www.clinicaltrialsregister.eu or http://www.ClinicalTrials.gov . This will not include information that could identify you. At most, the website will include a summary of the results. You can access the results of the study by visiting either website and searching for the study details included in this participant information sheet approximately one year after the trial has ended.

KEEPING YOUR DATA SAFE

How will we use information about you?

This next section describes how we will keep your data safe. In summary, it says that all parties involved in this study will treat your data in accordance with the law and best practise. Access to your personal data will be strictly limited to those who need it and will be kept strictly confidential. Your biological samples will be stored in secure locations with labels that cannot directly identify you and will be destroyed 25 years after the study finishes unless you consent to their future use.

Imperial College London is the sponsor for this study and will act as the data controller. This means that we are responsible for looking after your information and using it appropriately. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

The information we collect will include your National Insurance or passport number to allow us to search for you on the secure TOPS national trial volunteering database. This data will exclude any data linked with your samples, which will be kept by the study team for a maximum of 25 years. Undertaking any of the screening tests may result in us noticing something that could be important to your health. If so, we will contact you to explain what was noticed and support you with information regarding where to go for further advice. The study is expected to finish in June 2025.

For more information / confirmation regarding the end date please contact the study team, see **'Where can I find out more about how your information is used?'** for contact information.

People within the College and study team (see section sharing your information with others) will use this information to do the research or to check your records to make sure that research is being done properly and the information held (such as contact) details is accurate

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Some of your information will be sent to research partners based in countries in the European Economic Area or countries outside the European Economic Area. They must follow our rules about keeping your information safe. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

As a university we use personally identifiable information to conduct research to improve health, care and services. As a publicly funded organisation, we have to ensure that it is in the public interest when

we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

- Imperial College London - "performance of a task carried out in the public interest" - Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

Where special category personal information is involved (most commonly health data, biometric data and genetic data, racial and ethnic data etc.). Imperial College London relies on "scientific or historical research purposes or statistical purposes"

International Transfers

There may be a requirement to transfer information to countries outside the United Kingdom (for example, to a research partner, either within the European Economic Area (EEA) or to other countries outside the EEA. Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a UK adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient research partner that incorporates UK approved standard contractual clauses or utilise another transfer mechanism that safeguards how your personal data is processed.

Sharing your information with others

We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

- Other Imperial College London employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.). Imperial College London agents, contractors, and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third-party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

- Your GP – 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 them 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* (NTS).

- UK Health Security Agency and your local Health Protection Unit - We would inform the local health protection unit of your name, address and date of birth after you were challenged with

Salmonella (NTS). 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.

- The following Research Collaborators / Partners in the study
    - The University of Oxford – Collaborators based at the University of Oxford are providing statistical support to the study team. Outcome data (including the results of laboratory tests and/or genetic testing and/or transcriptomic data) may be shared to aid the analysis. All of data transferred will be anonymised.

Potential use of study data for future research

When you agree to take part in a research study, the information collected either as part of the study or in preparation for the study (such as contact details) may, if you consent, be provided to researchers running other research studies at Imperial College London and in other organisations which may be universities or organisations involved in research in this country or abroad. Your information will only be used to conduct research in accordance with legislation including the GDPR and the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you, used against you or used to make decisions about you.

Commercialisation

Samples and/or data from the study may also be provided to organisations not named in this participant information sheet, e.g. commercial organisations or non-commercial organisations for the purposes of undertaking the current study, future research studies or commercial purposes such as development by a company of a new test, product or treatment. We will ensure your name and any identifying details will NOT be given to these third parties, instead you will be identified by a unique study number with any sample / data analysis having the potential to generate 'personal data'.

Aggregated (combined) or anonymised data sets (all identifying information is removed) may also be created using your data (in a way which does not identify you individually) and be used for such research or commercial purposes where the purposes align to relevant legislation (including the GDPR) and wider aims of the study. Your data will not be shared with a commercial organisation for marketing purposes.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have because some research using your data may have already taken place and this cannot be undone.

- If you choose to stop taking part in the study, we would like to continue collecting information about your health from you, your hospital or your GP. If you do not want this to happen, tell us and we will stop. This will not affect any healthcare or support you may be receiving separately
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you if this could affect the wider study or the accuracy of data collected.

- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

If you do not wish the NHS to use your health records for the purposes of supporting any health-related research, please visit https://www.nhs.uk/your-nhs-data-matters/manage-your-choice to make your choice.

Where can I find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to the chief investigator m.gibani@imperial.ac.uk
- by going to our website pages (www.imperial.ac.uk/infectious-disease/research/human-challenge/chants)

Complaints

If you wish to raise a complaint on how we have handled your personal data, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk , via telephone on 020 7594 3502 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator

Data Protection and Privacy

All samples will be labelled only with your participant I.D. number. This means your personal data is partly anonymised (pseudonymised), so that those who get access to your samples cannot identify you. The only people who can link your I.D. number to you are doctors, nurses and other members of the study team who are working directly with you.

Your personal data will be held securely on a database, treated in strictest confidence, and will be held in accordance with data protection legislation. Access to personal information will be limited to authorised staff within Imperial College London, Imperial College Healthcare NHS Trust, and Chelsea and Westminster Hospital NHS Foundation Trust and regulatory authorities such as the MHRA. These organisations have a duty of confidentiality to you as a potential research participant.

Your records and personal information will be treated in the strictest confidence. You have right of access to any personal data being held by the study team. In the event of any inaccuracies recorded in the data, you have the right to request that such data be corrected. Please contact your study team using the contact details which you have been provided if you would like to view any of the personal data which is held about you or make use of any other right that you may have under applicable data protection laws.

Storage and use of samples and information from this study

The Sponsor and/or Imperial College Healthcare NHS Trust, and Chelsea & Westminster Hospital NHS Foundation Trust will keep all the biological samples and related data collected from you during the study to allow us to fully study and understand the disease. The Sponsor and/or Imperial College Healthcare NHS Trust, and Chelsea & Westminster Hospital NHS Foundation Trust will send your biological samples for testing in laboratories where they will be stored securely until the end of the study.

Your biological samples will be labelled with your study participant number and may contain your Year of birth, but we will not use your name or information that could identify you.

At the end of the study, some of your leftover biological samples and data from this study could be useful for other health research and laboratory testing. You will be invited to consent to storage of your samples for future use in other ethically approved studies. Any movement and storage of biological samples will be in accordance with the Human Tissue Act 2004 and other relevant laws in the countries they are sent to. You would not be told the results of such other research. You can still take part in the study if you do not want your leftover samples and information to be stored for future research.

Additional research may include genetic testing of the samples, for example to examine genes related to the immune system that may be involved in the response to *Salmonella* (NTS) infection. You will be invited to consent to the use of your samples for genetic testing. You can still take part in the study if you do not want genetic testing to be carried out on your samples.

What will happen to the results of the study?

If any results or publications are made publicly available during your participation in the trial, the study team will inform you where you can read these or provide you with a copy. If any results or publications are made publicly available after you have completed the trial, information about these can be found on the (www.imperial.ac.uk/infectious-disease/research/human-challenge/chants). You will not be identified in any report/publication.

Appendix

What tests will be performed at the screening visit?

- Full blood count
- Urea and electrolytes
- Liver function tests
- C-reactive protein
- Serum IgA
- Coeliac serology
- HLA-B27 screening
- Coagulation screen
- Haemoglobinopathy screen
- HIV 1&2 antibody
- Hepatitis B surface antigen
- Hepatitis C IgG
- Ultrasound of the biliary tract
- Ultrasound of the abdominal aorta.
- Malaria screen
- Urine pregnancy test
- HbA1c (test of blood sugar)
- ECG
- Resting heart rate, respiratory rate, blood pressure, oxygen saturations and oral temperature.
- Stool culture for *Salmonella* (performed after screening at Day-7 visit if enrolled).

Figures created with BioRender.com