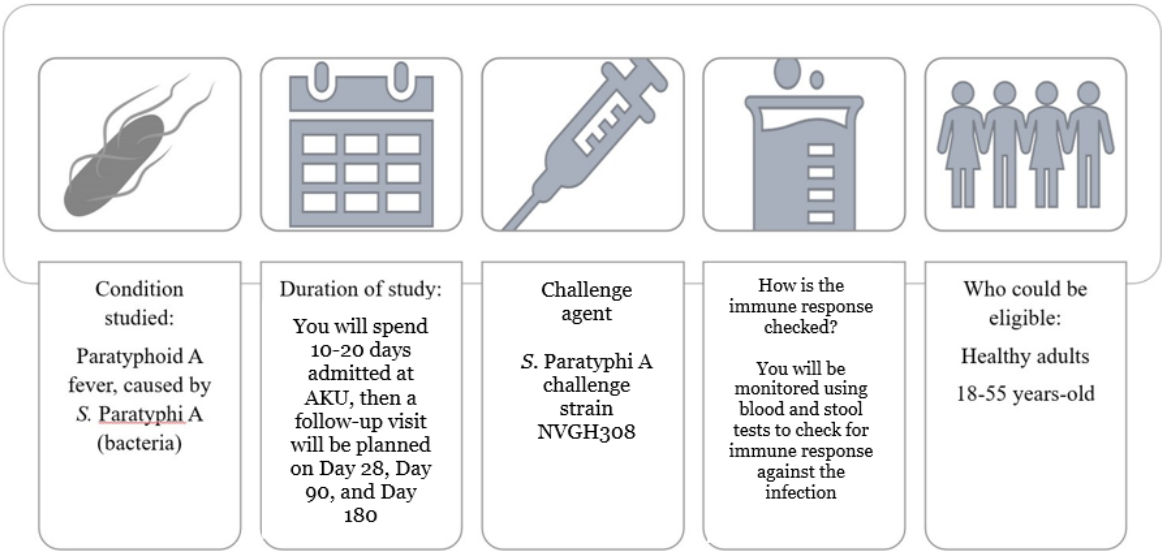
Salmonella Paratyphi A Controlled Human Infection Model in an Endemic Setting: Determining Safety, Dose Escalation, and Correlates of Protection

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study to investigate the dose of *Salmonella P*aratyphi A that is required to cause infection in humans in endemic regions and study how the body responds to this infection. This study uses a controlled infection model to learn more about immune responses, which may contribute to improved prevention strategies and vaccine development.

The Aga Khan University is conducting this study in Karachi, in collaboration with the Oxford Vaccine Group, which is part of the University of Oxford, and is funded by the Wellcome Trust. Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully and discuss it with others if you wish. If anything is unclear or you would like further information, please contact the study team. Participation in this study is entirely voluntary.

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



Contact details can be found at the end of this booklet

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OxTREC reference no. 1782933
AKU ERC reference no. 2025-11238-33974

Contents

	**Study site**	Aga Khan University
	**Location for challenge site**	Karachi
	**Principal Investigator**	Professor Farah Naz Qamar
	**Study Sponsor**	Aga Khan University. The sponsor takes on legal responsibility for the management of the research, ensuring the study is conducted in accordance with the protocol and good clinical practices.
	**Study Funder**	The Wellcome Trust
	**Who can take part in this study?**	We are looking to recruit healthy volunteers who are willing to stay at Aga Khan University, Karachi for 10-20 days and be available for all necessary visits, aged 18 to 55
	**What happens in this study?**	In this study we will be assessing what dose of *Salmonella* Paratyphi A is required to cause infection in people from endemic region and how the body responds to this infection.
	**Reimbursement**	You will be reimbursed for your 10-20 day in-hospital stay and for each follow-up visit on Day 28, Day 90, and Day 180. Payments will be made via cash.
	**Risks of participation**	Following challenge, you may develop paratyphoid infection; this will be carefully managed, and treatment is available. A full discussion of the risks can be found in this document.
	**Benefits of participation**	By taking part in this study, you will help research into the dose of *Salmonella* Paratyphi A required to cause infection in endemic regions, the body's immune response to this infection, and in the potential development of a new vaccines against *Salmonella* Paratyphi A. You will not directly receive any other personal health benefit from the study or its procedures.

What is the purpose of this study?

In this study we will be assessing what dose of *Salmonella* Paratyphi A is required to cause infection in adults of endemic region and how the body responds to this infection using Controlled Human Infection Model (CHIM)

We are looking to recruit up to 60 healthy volunteers aged 18-55.

What are *Salmonella* Typhi and Paratyphi A?

Typhoid and paratyphoid fever are both forms of an illness called Enteric fever. Their names come from the bacteria that cause them: *Salmonella* Typhi and *Salmonella* Paratyphi. *Salmonella* Paratyphi A is thought to be responsible for almost all cases of paratyphoid fever. Although they are from the same family as the *Salmonella* bacteria that causes gastroenteritis (for example food poisoning) in Pakistan, they are quite different.

Enteric fever causes individuals to feel generally unwell, sometimes with high fevers, headache, muscle and joint aches, abdominal pain and constipation. If severe or left untreated, it can result in complications, long-term carriage of the bacteria or death.

There are approximately 13 million cases of Enteric fever every year. Over two thirds are due to typhoid, for which there are vaccines available. Just under a third of cases (approximately 3.8 million per year) are due to paratyphoid, for which there is no vaccine. Both typhoid and paratyphoid are spread by the faeces of an infected person, typically via contaminated water or food. They are found in parts of the world where people don't have access to clean water and sanitation, including in Pakistan.

Where is this study taking place?

The study is taking place at the Aga Khan University (AKU) Karachi. The challenge will be administered at AKU where you will be admitted for 10-20 days. After you are discharged from the hospital, further follow-up appointments will take place at AKU as well. Travel will be arranged by the study teams and time expenses will be reimbursed.

Are there vaccines against *Salmonella* Paratyphi A?

There are currently no licensed vaccines against *Salmonella* Paratyphi A. However, there are effective vaccines to protect against *Salmonella* Typhi which are licensed and widely used in Pakistan.

What is a Controlled Human Infection ('challenge') Study?

Controlled Human Infection or challenge studies involve deliberately exposing participants to an infectious agent (such as a bacterium). We will be asking participants to drink a solution that contains bacteria. 'Challenge' using bacteria that cause enteric fever (*Salmonella* Typhi and *Salmonella* Paratyphi A) has been performed safely at the Oxford Vaccine Group since 2011. Around 500 participants have been involved in these studies. Many such studies have been conducted throughout the world and they play an important role in the development of vaccines.

Human challenge is done in a very controlled way using a specific dose.
Participants are then closely monitored for signs of infection. All participants are treated with antibiotics at the end of the observation period, regardless of whether they develop signs of infection, to make sure that the challenge bacteria are eradicated. This type of study is very powerful as it can be used to look at diseases that are hard to study when they occur naturally.

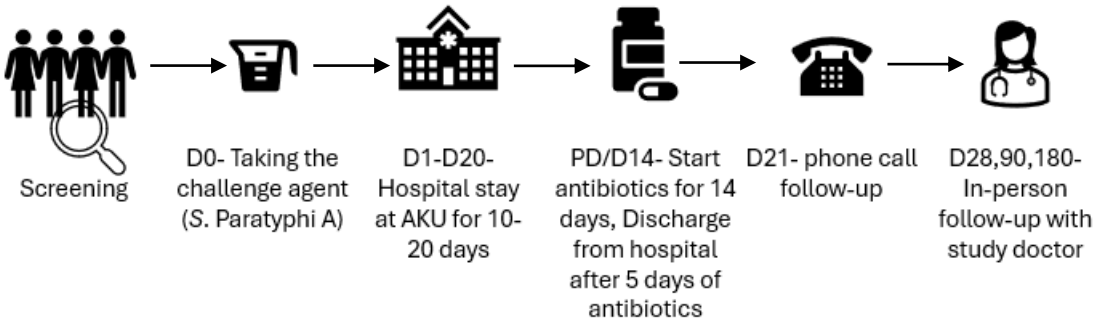
For this challenge study, AKU will use *Salmonella* Paratyphi A. We will investigate the dose of *Salmonella* Paratyphi A that is required to cause infection in adults from Pakistan, which is an endemic region. We will admit participants in groups of 3-5 and start with the dose of challenge agent which has been used in UK (non-immune population) and increase the dose in each group till an effective dose causing infection is determined.

Why have I been invited?

We are looking to recruit healthy volunteers who are aged between 18 and 55 years.

What does this study involve?

The following diagram gives a simplified outline of the key study visits and what will be done during each visit.



Please note that you must be willing to stay at AKU for the duration of challenge period till at least 5 days after starting antibiotics, or till at least day 10 post challenge, whichever is longer and be available for all follow-up visits at AKU after discharge.

Staying in the hospital after consuming the challenge agent is crucial to allow close monitoring for any symptoms and to prevent the risk of transmitting the infection to others. Since *Salmonella* Paratyphi *A* can spread in unhygienic conditions or through inadequate sanitation systems, this measure is essential to optimize infection control.

Additionally, it is vital to remain in contact with the study team after discharge to ensure completion of treatment and adherence to follow-up visits.

Follow up visits would then be on Day 28, Day 90, and Day 180 after 'challenge' day. The total study duration would be approximately 6 months. You must agree to comply with the requirements of the study.

If you develop Paratyphoid infection, additional samples are planned after 14 days of antibiotics are completed.

Do I have to take part?

No. Taking part is entirely voluntary. We are looking for volunteers. Should you volunteer and later change your mind (for whatever reason) it is your right to do so and you would not need to provide an explanation to the study team or anyone else, but because of the nature of this study you may need follow up and treatment even if you chose to withdraw, depending on the stage of the study you were at when you chose to withdraw.

Whatever you choose it is important that you are happy with your decision, and it is not the role of the study team to decide for you. We would help present the details of the study and answer all your questions so you could make an informed decision.

If you decide not to participate in the study or discontinue the study participation, this will not affect your standard medical care.

Who can take part in the study?

We are looking to recruit volunteers who are healthy and aged 18 to 55. Volunteers need to be available for all necessary visits and stay at the Aga Khan Hospital for initial 10-20 days of the challenge period including at least 5 days after starting antibiotics.

Certain things may mean you are **not able to take part** in the study, which will be explained in the section below.

When Am I Not Eligible to Participate in the Study?

Pregnancy

Paratyphoid infection can potentially be dangerous during pregnancy both to the mother and to the unborn child. Participants that can get pregnant will therefore be asked to use an effective method of contraception after being discharged from the hospital. It is a requirement of participation that volunteers who could become pregnant must use contraception. Exceptions to this are below:

- Absence of female reproductive system

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- Post-menopausal
- Surgical sterilisation.

Acceptable contraception methods include:

- Oral, injected or implanted hormonal contraceptives that prevent ovulation
- Intrauterine device (IUD)
- Intrauterine system (IUS)
- Sole sexual partner is a vasectomised male
- Barrier methods of contraception
- Complete abstinence from sex with a male partner for the whole duration of the study**.**

Other reasons not to be able to take part

- History of any **significant medical condition**, such as diabetes (amongst others)
- Any known or **suspect immune system impairmen**t or function abnormality such as **HIV infection**, **auto-immune conditions** (like Graves or coeliac) or history of **cancer** (except some types of skin cancer)
- **Gallbladder problems**, like stones or polyps or surgical removal of gallbladder in the past
- Presence of **implants or prosthetic material**, like screws/pins/plates
- Moderate or severe **depression or anxiety** or other uncontrolled **mental health condition**s
- Weight less than 50 kg
- If you are taking certain medications on a regular basis, that could affect the study outcome.
- Contraindication to any of the antibiotics used in the study (ciprofloxacin, cefixime, azithromycin, co- trimoxazole or ceftriaxone)
- Family history of **aneurysm**
- Scheduled **elective surgery** or other procedures requiring general anaesthesia during the study period
- Abnormal results from screening investigations (please see in the section “Face-to-face screening visit” which tests are done at screening).

There are also some situations in which we may need to delay the start of the study for you.

If you are unsure about any of the conditions listed, a member of the study team can help you.

We would also like to know if you are expecting to receive any vaccines during the study period as this may affect whether you are able to participate in the study.

What will happen to me if I decide to take part?

If you choose to take part, you will sign a written consent for after which you will be screened for the applicable eligibility study criteria. If found eligible, you would be involved in the study for approximately 6 months in total. The different stages of the study will now be outlined in detail.

Study Procedures

Prescreening:

Our researchers will explain the study's aims and objectives and provide details about your participation. They will assess your eligibility by asking some basic questions. If you qualify based on the pre-screening questionnaire and are interested in participating, you will be invited to AKU for a more detailed discussion.

Face-to-Face Screening Visit (Up to 2 hours)

The purpose of screening is to assess whether you can participate in the study. This visit will occur at AKU.

At the screening visit, we will outline the nature of the clinical study in person, and this will explain what to expect by taking part, the risks involved and what side-effects you might expect to experience. This visit would provide an opportunity for you to ask any further questions you might have to a member of the study team and what is involved. You would be allowed as much time as you needed before making any decision on whether or not to take part.

If you choose to proceed, you will receive a consent form. A researcher will review it with you. Study procedures will only begin after you have signed the informed consent form.

We would ask you questions about your health, undertake a physical examination including an ECG ('heart tracing') and take urine and blood samples. We would also arrange an ultrasound scan of your gallbladder to check for any abnormalities (e.g., the presence of any gallstones would mean you would be unable to take part). This is a non-invasive and painless procedure.

Blood would be screened for general health (to check your blood count, kidney, and liver function), HIV, hepatitis B and C and coeliac disease as well as for a congenital immune deficiency that some people have without knowing (called IgA deficiency). Your blood would also be tested for the presence of the HLA-B27 gene, which can be associated with some autoimmune conditions. All participants are also asked to complete a mood assessment to screen for anxiety and depression. Urine will be tested for the presence of blood, protein, and glucose. For all participants of childbearing potential, we would also perform a pregnancy test on your urine sample.

Following the screening tests if an abnormal result was found on one of the tests, we would discuss this with you. We may provide you with the information and ask you to attend your GP.

If the study team found any reason why you could not take part in the study, this would be discussed with you.

Once the study team have confirmed your suitability for the study, we will inform you and arrange a date for your challenge visit. If more than 120 days have elapsed from your screening visit to vaccination, we would repeat your face-to-face screening visit, including some of the procedures.

Your participation in this study is at the researchers' discretion.

Is coming to screening a commitment to taking part?

No. It is an opportunity to meet with the study staff and ask questions. You do not need to decide there and then.

Overview of the Study

This diagram shows an overview of the whole study. This information booklet will now go through each part of the study in detail.

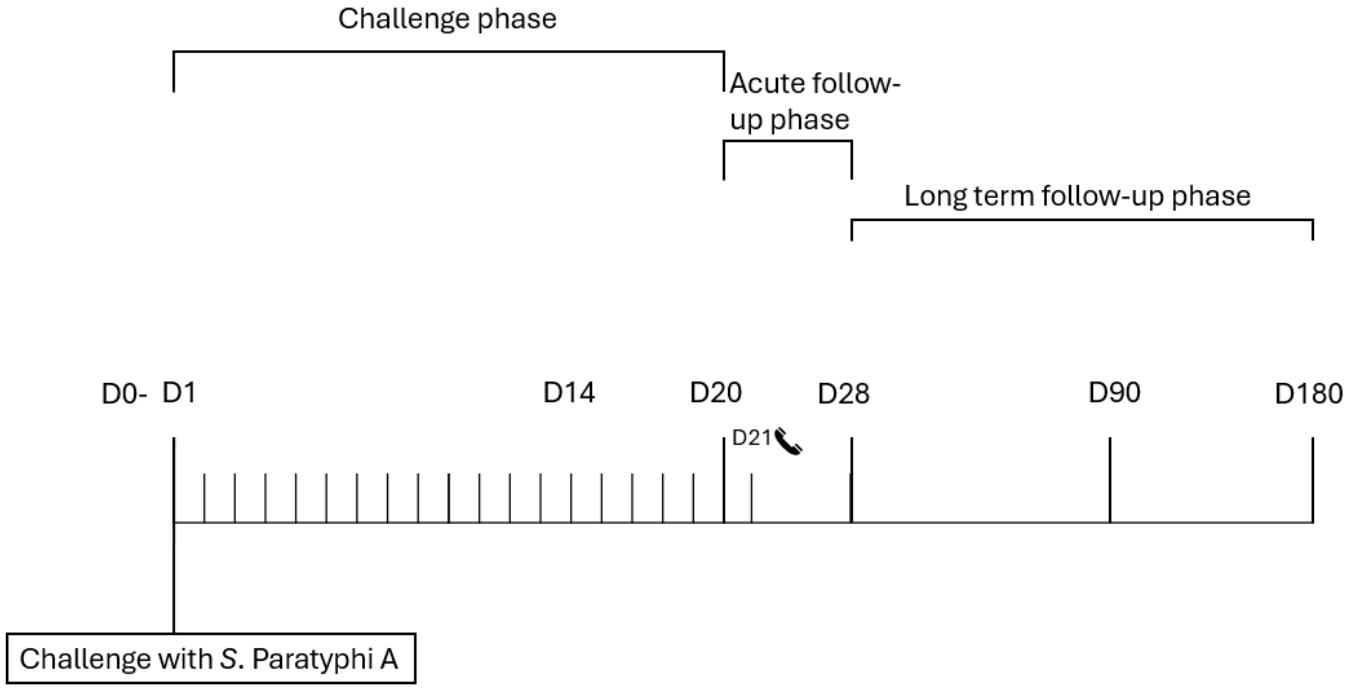

Figure 1: Study overview

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Challenge day (Day 0) - Start of the intense monitoring period

The challenge visit would take place at AKU under controlled conditions. We will admit volunteers in groups of 3-5. We will increase the dose of *Salmonella* Paratyphi A in each group to determine the optimal dose that is required to cause infection.

On the day of challenge, you would be asked to fast (i.e., not eat or drink anything) for 90 minutes before the appointment time.

We would first give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella* Paratyphi A) followed by the drink containing *Salmonella* Paratyphi A bacteria. You would then be asked to fast for a further 90 minutes. Once the 90 minutes are complete, lunch would be provided for you. You should remain at AKU for a period of 10-20 days. You will be provided accommodation at AKU with 3 meals per day. To ensure your safety you will be monitored by nurses and doctors throughout your stay. The study team will document any symptoms you may experience during this time. Any vomit within 2 hours after the challenge is administered would contain paratyphoid and would require careful cleaning. If vomiting did occur, you would need to be treated with antibiotics and kept in the study only for safety reasons (withdrawn from protocol-specified procedures).

For the 14 days following challenge (or until you are diagnosed) 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 Paratyphoid A infection. Your study doctor can give you options of medications to reduce pain if needed. We would also ask you to follow strict hygiene measures until we confirm clearance, that usually happens around 6 weeks after challenge, but may take longer. Clearance is confirmed after 3 stool samples collected at least one week after completing antibiotics are tested negative for *S.* Paratyphi A.

What happens at the follow-up visits?

The first follow-up call will take place on Day 21, followed by in-person visits on Day 28, Day 90, and Day 180. Additionally, we may request an unscheduled visit if there are any safety concerns. You can contact us on the telephone at any time if you are concerned about any medical conditions

It is important that you are available to attend all scheduled follow-up visits after being discharged from the hospital, along with any additional visits that may be requested on short notice if you develop symptoms that the study physician believes require an in-person evaluation.

What happens if I get Paratyphoid A infection?

The main symptom of paratyphoid infection is fever (a high temperature). Some people will also feel generally unwell or very tired, have a headache, have muscle or joint aches, go off their food, have stomach pain, and/or feel sick, like they had a very bad flu. If your temperature remains high for 12 hours or if we

found bacteria in your blood tests, then you would be diagnosed with paratyphoid infection. You will then be immediately treated with a course of antibiotics to clear the Paratyphoid infection.

Once you have started the course of antibiotics, paracetamol can be taken to lower your temperature, which we will provide. If you develop Paratyphoid A infection, you could feel unwell for several days. The majority of participants who develop Paratyphoid infection in this setting, have only limited or mild symptoms, we do not expect you to become severely unwell during this time. However, we will monitor you in the hospital to ensure the infection is managed safely.

For safety reasons, we would need more frequent testing with blood and stool tests when you are first diagnosed and then at 12 or 24 and then at 48, 72, 96 and 120 hours later. These tests will ensure that you are responding well to the antibiotic treatment. You will stay at the hospital for at least 5 days after the antibiotics have started or till day 10 post-challenge (whichever is longer) and should be fever free before being discharged. Additional visits may be required for your safety and the study team will talk to you about these. Blood and stool samples may be sent to collaborating laboratories to confirm standard of results. Please check the section on the risks of taking part for more information.

What happens if I do not get paratyphoid infection?

If you are not diagnosed as having paratyphoid infection, at day 14 after challenge we would still give you a course of antibiotics. This is to ensure *Salmonella* Paratyphi A bacteria are eliminated from your body. You will take the antibiotics for 14 days and will be discharged home after 5 days of antibiotics (but not before day 10 post challenge).

What antibiotics will I be taking and what are the potential side effects?

We will use ciprofloxacin. It is available as tablets; ciprofloxacin is taken as one tablet every 12 hours for 14 days. It is recognised as being appropriate treatment for paratyphoid infection and is widely used for treatment of many different types of infections. In order to monitor your response to antibiotics and any potential side effects, you would be in contact with the study team and complete follow-up visits. If you were to develop any symptoms after going home, you would contact us. We would be able to advise you on the most appropriate course of action, which might include switching you to an alternative antibiotic.

Most people do not have any side effects from these antibiotics. General side effects of antibiotics can sometimes occur. These might include upset stomach, nausea, vomiting, diarrhoea, headache or thrush. Occasionally, ciprofloxacin can cause a rash, dizziness or itching and changes in the liver or kidney blood tests. Very rarely ciprofloxacin causes sensitivity to sunlight, seizures, problems with the blood cells (reduced white cells or platelets), ringing sound in the ears, joint or muscle pains, tendon inflammation or areas of numbness/pins and needles. It can also trigger or worsen depression, or make people feel confused, or experience hallucinations or other strange sensations.

We will discuss these with you at your screening visit and would ask you to monitor for any of these symptoms (in particular: tendon pain, numbness of hands/feet, worsening mood) and let us know immediately if you develop any of them. If you do not show improvement after 5 days of taking Ciprofloxacin, an adult Infectious Diseases specialist on the study team will assess your condition and advise second-line antibiotics (intravenous Ceftriaxone) or third-line antibiotics (oral Azithromycin or intravenous Meropenem). Your response will be monitored closely.

Participants using oral hormonal contraceptives ('the pill') should use additional barrier contraception (such as condoms) during the challenge period until shown to have cleared the bacteria (approximately 3 months in total), in case absorption through the gut lining has been affected by the bacteria from the challenge or by the antibiotics use.

The amount of antibiotic that is absorbed can be affected by antacids and iron supplements. We would therefore ask you not to take these whilst you were taking the antibiotics.

It is possible that Paratyphoid A exposure and the antibiotics used to treat the infection have a transient effect on your gut and the balance of bacteria that naturally live in your body. One aspect of this study will be to look at the effect of these on the bacteria in the stool.

Will I need to take any other medicines?

Some people may experience symptoms after being 'challenged' and, if required, the study doctor can prescribe medication to help with these (e.g., laxative for constipation). Any such medicine, including its benefits and side effects, will be discussed with you beforehand.

In certain circumstances it is acceptable to continue to take long term medications (e.g., the 'pill') – one of the study doctors would discuss this with you during screening. If during the study any other treatment became necessary, it would be important to inform us immediately so that we could ensure that the antibiotics and treatment you had been given were safe. We would ask you to inform us of all the medications (including vaccines) that you took during the study, which will include keeping a record of the medications you take.

What samples will be collected?

We would take blood and urine samples as part of the screening visit, to help us assess your general health. Stool samples would be collected at the study visits after the challenge and until clearance, for safety reasons, and some participants may also be asked to provide stool and saliva samples at some other visits. Some of the samples are for research tests and we would not be able to provide these results, but we can 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 paratyphoid infection or not. Total blood volume taken will not exceed that of two blood donations. including in-patient time and out-patient follow-ups (the limit in a year is three donations for both men and women, according to the Sindh Blood Transfusion Authority). For this reason, participants will be asked not to donate any blood while participating in the study.

What will happen to the samples I give?

We will collect samples throughout the study to check your health and monitor your immune response.

Sample Storage: Your samples will be safely stored and labelled with a code instead of your name or other details. This is done to protect your privacy.

Sharing Samples: Samples may be shared with other researchers in different countries including the UK, and possibly others. This will help learn more about how the body's immune system responds to infections, improve methods for diagnosing and detecting infectious diseases and development of effective vaccines. This research may involve commercial organisations.

Future Research: We would like to store your samples in Pakistan and the UK after the study has finished to help future research. This is optional though and you can say no to this and still take part in the study. Samples would be stored for up to 07 years but may be longer if ethics committee agrees.

Genetic Testing: We will test some of your genes (DNA) to see how your immune system responds to infections. Although samples will be stored with a code instead of your name or other details, your DNA is unique to you so it can never be made completely anonymous.

Duration of sample storage: Your samples may be stored at the AKU Biorepository for up to 7 years (or longer with approval from the ethics committee) and at the Oxford Vaccine Center (OVC) Biobank indefinitely. Oxford Vaccine Group has been collecting samples from study participants for over 30 years and has an ethically approved Biobank. Your samples from this study will only be stored in the OVC Biobank if you voluntarily give your consent.

If you choose not to allow storage of your samples in the biobank or biorepository, you can still fully participate in the study without any problem.

Would any genetic tests be done?

Some blood would be used to look at the pattern of genes being actively used by your body in response to the *Salmonella* Paratyphi A infection. The response to infection is in part genetically controlled, so knowing the pattern of genes that are being used may help us to understand how individuals respond to vaccination and paratyphoid infection. Additionally, we would study the effect of different antibiotics on bacteria

present in your stomach, for this purpose, extra stool samples collected on specific time points throughout the study for microbiome testing using gene sequencing.

What else do I need to know?

If you choose to take part in this study, we will be asking for your permission to store your samples in a collection of samples called a 'Biobank'. (University of Oxford) and Biorepository (AKU) you are free to say no to the Biobank/biorepository and continue to take part in this study if you wish.

Should you consent to this, you will NOT be asked to donate extra samples and you will NOT be asked to undergo any extra procedures. All samples will be stored in a de-identified way.

What if we find something unexpected?

If abnormal results or undiagnosed conditions are found during the course of the study these will be discussed with you (we would not report them to anyone else without your permission). For example, a new diagnosis of high blood pressure might be made or if we found you to be positive for infections such as Hepatitis B or C or HIV. We will guide you regarding further referral in this case.

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, but this is not a health check. We hope that the knowledge gained from this study will contribute to the understanding of Paratyphoid disease. We cannot guarantee however that you will be protected from these infections either during the study or in the future.

Are there any disadvantages or risks from taking part?

Risks of undergoing challenge

The risks of taking part in this study are very low, provided that you comply with study visits and maintain close contact with the study team as outlined in this booklet. Your stay at the hospital is to ensure that the infection is carefully managed, and you do not pass this infection to anyone else. If untreated, paratyphoid infection can result in serious illness or even death. However, around 500 people have been successfully challenged with *Salmonella* Typhi and Paratyphi A bacteria that cause enteric fever at the Oxford Vaccine Group since 2011, and all have made a complete recovery from infection.

Paratyphoid Infection

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

- fever
- chills
- headache
- feeling tired and generally unwell
- muscle or joint aches
- abdominal discomfort
- nausea or vomiting
- loss of appetite

You will need to stay at the hospital at least 5 days or till day 10 (whichever is longer) after the antibiotics have been started and should be fever free at discharge. For this you will need to take time away from work.

Severe problems are unlikely, as we would treat participants very early on in the course of illness (immediately after developing persistent fever or if a participant has bacteria in their blood tests). Severe complications are rare and mainly occur when paratyphoid fever is not treated properly or timely. If paratyphoid fever is left untreated, possible complications include bleeding from the gut, a hole developing in the gut, becoming a carrier of paratyphoid, altered consciousness, coma, or death. It is for these reasons that it would be crucial that you take the full course of antibiotics, stay in contact with the study team and complete all follow-up visits. There is also a small risk of relapse, when the infection may happen again within 2-4 weeks, after completing treatment. In the unlikely event this were to happen, you would require a second course of antibiotics. For this reason, if you develop a fever even after completing treatment, it is important to communicate with the study doctor.

Excretion of bacteria in the stools

A small percentage (up to 10%) of people who contract paratyphoid infection can go on to carry the bacteria and excrete the bacteria in their stools for 3 months or even longer periods. These people are known as ‘carriers’ and we know that people with gallstones are especially vulnerable to becoming carriers. For this reason, we would do an ultrasound scan of your gallbladder at screening and if we found that you had evidence of gallstones, you would not be able to take part in the study.

We also collect 3 stool samples after you have completed your antibiotics to prove that the paratyphoid bacteria have been fully cleared from your body (called clearance samples). Rarely, stool cultures can remain positive even after you have completed a course of antibiotics. In the unlikely event that this were to occur, you would receive further antibiotics to significantly reduce the risk of you becoming a carrier.

Antibiotics

A small number of people may have side effects to the antibiotics used to treat the paratyphoid infection. We will discuss these with you when you come to screening. There is further information in the section above called ‘What antibiotics will I be taking and what are the potential side effects?’

General risks

This study involves blood tests during hospital stay and at all visits. Taking blood samples may sometimes result in bruising to the area and some people can feel faint. It is also possible that due to the volume of blood taken in the study you may become anaemic; your blood tests are closely monitored for this. Staying at the hospital poses a risk of catching hospital acquired infections. For this reason, strict infection control measures will be in place.

Can I give paratyphoid infection to anyone else?

Paratyphoid infection is transmitted to other people through them coming into contact with the faeces of infected individuals. This would only occur following poor hygiene practices such as not thoroughly washing hands after using the toilet and before preparing food. Most cases occur within a household and other close contact situations (e.g., sexual contact) but transmission is extremely unlikely if good hygiene practices are followed. We will discuss this with you at screening.

This is another reason you are required to stay at the hospital after challenge administration and when you develop infection, for at least 5 days of antibiotics, until fever free or till day 10 post-challenge, whichever is longer. After discharge you will need to observe some precautions you will need to observe these precautions till 3 follow-up stools cultures are negative.

These “enteric precautions” include:

1. Hand Hygiene

- Wash hands thoroughly with soap and water for at least 20 seconds after using the restroom, before eating, and before preparing food.
- Avoid touching your face, especially your mouth, nose, or eyes, without clean hands.

2. Sanitation Practices
   - Ensure proper disposal of human waste in a sanitary manner.
   - Use clean, functional toilets and avoid open defecation.
   - Clean and disinfect toilet seats, flush handles, and bathroom surfaces regularly.
3. Food and Water Safety
   - Consume only properly cooked food and drink safe, treated, or boiled water.
   - Avoid raw or undercooked foods, particularly seafood and street food in areas with poor sanitation.
   - Wash fruits and vegetables thoroughly, ideally with clean water.
4. Isolation Measures
   - Infected individuals should avoid preparing or serving food for others until they have completed treatment and are cleared by a healthcare provider.
   - Avoid sharing utensils, plates, or cups with others.

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In summary:

This study involves:

- Drinking a solution containing a strain of *Salmonella* Paratyphi A which causes Paratyphoid fever.
- The aim of the study is to see what dose of *Salmonella* Paratyphi A will cause infection in adults of Pakistan and to study the body's immune response to infection.
- 3-5 participants will be enrolled in each group, we will start with a low dose of *S.* Paratyphi A and increase the dose which each group until the appropriate dose that causes infection is determined.
- Staying at AKU for 10-20 days during challenge phase and at least 5 days after starting antibiotics. After discharge complete all planned follow-up visits (Days 28, 90, and 180)
- Having blood, and sometimes saliva and stool samples taken during hospital stay and at visits. The approximate study duration is 6 months.

What is expected of me during the study?

- You will need to stay at AKU for 10-20 days after having the challenge agent.
- You need to attend all study visits on Days 28, 90, and 180.
- You will need to travel to a challenge site (AKU Karachi).
- You must remain in mobile telephone contact throughout the study.
- You must stay in close contact with the study team throughout the study.
- You must nominate someone who lives near to you and who would know where you were for the duration of the study as an alternative contact for the study team. You would give this person the study information and ask them to return a signed reply slip with their details and a 24-hour phone number. If for any reason we could not get hold of you or your 24-hour contact during the study and were concerned about your welfare we may visit the place you are staying and/or call the Police.
- After *Salmonella* Paratyphi A challenge, you must not take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to do so by a study doctor.
- You must take a full course of antibiotics when given to you.
- Participants that can get pregnant should use an effective method of contraception from one month prior to vaccination until they are shown to be clear of *Salmonella* Paratyphi A bacteria.
- Participants using oral hormonal contraceptives (e.g., the "pill") should use additional barrier contraception (such as condoms) during the challenge period until shown to have cleared the bacteria (approximately 2-3 months in total).
- You must provide at least 3 stool samples after the completion of antibiotics so we can ensure you are clear of paratyphoid. These would be obtained 1 week after you completed antibiotics and would be collected at least 48 hours apart.
- You must follow strict hygiene measures from challenge day until clearance is confirmed.

Will my taking part be kept confidential?

Yes. All information that is collected about you during the course of the research would be coded with a study number and kept strictly confidential. Any information about you that leaves the clinic would have your name and address removed so that you could not be recognized. The following groups may inspect study records without violating your confidentiality:

Monitors who check that the study is being conducted to a high standard, including the Data and Safety Monitoring Board(DSMB) - an independent panel of experts responsible for study safety.

Pseudo-anonymised data and samples would be sent to other researchers working with us on this research project. The data and samples would be pseudo-anonymised, this means that information from which you could be identified has been removed and stored separately from the dataset or samples which are shared with these researchers. Therefore, these researchers would not receive your personal data.

How much will I get paid?

All participants will be reimbursed for their time, travel and for inconvenience.

Payments are made directly by cash at the end of challenge period (inpatient stay) and on each follow-up visit.

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 study.

Where can I get advice on whether to take part?

We are happy to answer any questions you might have and contacting us does not commit you to taking part in the study. Please feel free to contact us on:

Prof Farah Naz Qamar
Phone: +922134865035
Email: farah.qamar@aku.edu
Dr Saba Siddiqui
Phone: +922134869674
Email: saba.anwer@aku.edu

What will happen to my data?

For those participants who proceed to take part in the study, the data from the screening questionnaire will be kept with their study records. For those who do not proceed to participate in the study, all answers from

the screening questionnaire will be kept until the end of the study recruitment period and then will be deleted. If you supplied your medical history or underwent screening but were not given the challenge in

the study either because you were not eligible or decided not to take part, then any data collected will be kept until the end of the study.

Responsible members of AKU and study monitors may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. You will be given a study number, which will be used on study paperwork and samples. We will be using information from your medical records in order to undertake this study and will use the minimum personally identifiable information possible. We may need to view and record your ID (CNIC) number. This will be taken at the screening visit. We will securely retain this information until the end of the study.

The Aga Khan University and the University of Oxford are a 'joint data controllers' and are responsible for looking after your information and using it properly. Aga Khan University will use your personal information to contact you about the research study and make sure that relevant information about the study is recorded for your care in relation to your health during the study, and to oversee the quality of the study. Your personal information will be kept confidential and handled in accordance with data protection laws in Pakistan.

Study staff will ensure that participants' data is pseudo-anonymised. Participants will be identified by a participant ID number on the study paperwork.

We may disclose this data to our collaborators and monitors to carry out activities specifically for the purpose of this research study and as explained in this information sheet.

Study data may be stored electronically on a secure server by the AKU IT team and paper notes will be kept in a secure location at the study site. We will store the research data and any research documents that contain personal information, such as consent forms, securely for up to 7 years after the end of the study, or as per national regulatory requirements. Anonymised research data may be kept indefinitely. It will not be possible to identify you in any publication or report.

You can stop being part of this study at any time, without giving a reason, but we will keep information about you that we already have, including samples. If you prefer, you can request that your samples are destroyed (if they have not already been analysed).

If you have agreed that samples can be retained for future research, then your personally identifiable information will be kept with restricted access solely for the purposes of sample management. Samples will be provided for future research only in a form that does not identify you.

At the completion of the study, unless you consent otherwise (e.g., if you request to be informed of other studies), your personal details will not be used to contact you other than exceptional circumstances concerning your safety. If you consent to take part in another study carried out by AKU, personal

information and medical information including blood test results may be accessed to avoid unnecessary repetition.

If you agree to future contact (e.g. to be informed of other studies) we will continue to store your consent form within the study records and personal information (e.g. name, DOB, contact details) in a password protected database. This will be archived on a university server with restricted access and kept indefinitely, or until the study team feel that it would no longer be required, at which point it will be deleted. This will be held separately from the study data and you can request at any time to have your details removed. If you have not consented to be approached for future studies, your contact details and consent form will be destroyed after 7 years as per national regulatory requirements.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. You can find out more about how we use your information:

- By asking one of the research team
- By sending us an email to: farah.qamar@aku.edu, saba.anwer@aku.edu
- By ringing us on:
  +922134865035
  +922134869674

What will happen if I do not 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 at any time without giving a reason.

If you wish to leave after drinking the challenge (*Salmonella* Paratyphi A) bacteria, then you would need to:

- Take a full course of antibiotics.
- Provide 3 stool samples one week after completing the antibiotics to demonstrate clearance.

The reason for this is to ensure you would be treated and free of the bacteria, as very serious consequences can occur in individuals with untreated paratyphoid infection.

If you withdraw from the study after we have collected samples from you, unless you state otherwise, any biological samples, which have been collected whilst you have been in the study, will be used for research as detailed in this participant information sheet.

What if there is a problem?

The investigators recognise the important contribution that volunteers make to medical research and will make every effort to ensure your safety and wellbeing. If something does go wrong, you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further clinical action and refer you to a doctor.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact the numbers mentioned above.

Who is organising the funding?

This study is funded by the Wellcome trust

Who has reviewed the study?

The study has been reviewed by the study sponsor and primary site the Aga Khan University (AKU) . It has been approved by AKU Ethical Review Committee (ERC), the National Bioethics Committee (NBC) of Pakistan and Oxford Tropical Research Ethics Committee (OxTREC) in the UK.

What will happen to the results of the study?

The results of the research will be published on the University of Oxford website, AKU website, presented at conferences or published in a scientific medical journal(s), which can potentially take a few years. All publications will be available online.

Your individual results would not be identifiable, nor would you be identified in any report or publication.

The results of the research and the data generated by the research will also potentially be used for future academic research.

What do I do now?

Thank you for considering taking part in this study.

If you do not wish to participate in the study, you do not need to contact us. If we do not hear from you, we will assume that you do not want to take part in the study. However, you are welcome to contact us using the contact details below if you wish.

If you are interested in participating in the study, you do not need to make a final decision straight away. If you wish to discuss any element of the study further or clarify any doubts, please consider:

- Contact us using the contact details below:

+922134865035 (Prof Farah Naz Qamar)

+922134869674 (Dr Saba Siddiqui)

Yours sincerely,

CI/PI signature

CI/PI Name: Prof Farah Naz Qamar

Site: AKU Karachi