Informed Consent Form

Study Title:

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

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Participant Information

Participant ID	
Participant Name	
Father/Husband Name	
Date of birth	
Age	
Gender	
City	
Complete address	
Contact: Landline Cellphone Alternate contact	
CNIC number	
Name of researcher taking consent	

You are invited to participate in a research study designed to understand how the body responds to *Salmonella* Paratyphi A infection, a bacterium that causes paratyphoid fever. This study uses a controlled infection model to learn more about immune responses, which may contribute to improved prevention strategies and vaccine development. Before deciding, please read the information below carefully and ask any questions you may have.

Controlled Human Infection Model (CHIM)

Controlled Human Infection Model (CHIM) studies involve exposing healthy volunteers to specific germs in a safe and controlled environment. These studies help researchers understand how diseases spread, how germs cause illness, and how the body fights infections. They are also used to test the effectiveness of vaccines and medicines in preventing or treating these diseases. CHIM studies have been conducted for many years and have significantly contributed to improving treatments and preventing diseases worldwide.
The bacteria used in these studies are carefully tested in laboratories to ensure they are sensitive to commonly available antibiotics, and easily treatable. Participants are closely monitored throughout the study to prevent complications, and because of this rigorous oversight, serious side effects have rarely been reported.

Purpose of the Study

The primary goal of this study is to determine the dose of *Salmonella* Paratyphi A that causes paratyphoid infection in healthy adults and to investigate the body's immune response to the infection in a population that is pre-exposed to Paratyphi. Your participation will help researchers understand how the body's immune system responds, which could improve methods for diagnosing and detecting the disease and aiding in the development of effective vaccines.

Study Procedures

If you choose to participate, you will undergo these steps:

Screening and Initial Assessment:

You will undergo a physical examination, blood tests, Electrocardiography, an ultrasound of the Abdomen, and a medical history review to confirm that you are healthy to be able to take part in the study. Summary of screening procedures is provided in table 1.

Table 1 list of lab tests and other screening procedures

Screening procedures
Blood tests: 1. Complete Blood Count (CBC) 2. Urea 3. Electrolytes (serum Sodium and Potassium levels) 4. Creatinine 5. Liver Function Tests (bilirubin, ALT, ALP) 6. Albumin 7. Amylase

8. C-reactive protein 9. Serologies: HIV, HBsAg (Hepatitis B), HCV (Hepatitis C) Antibodies 10. TTG and IgA level 11. HLA B27 **12.** Blood glucose (random)
Urine tests: 1. Urine dipstick **2.** Urine pregnancy test (if applicable)
12 Lead ECG
Ultrasound scan gallbladder
Mood assessment (using HADS questionnaire**)**
Physical examination by study doctor including vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation)

Controlled Infection with Salmonella Paratyphi A:

If your tests are reported normal, and you agree to take part in the study, you will be admitted at the Aga Khan hospital where you will be given a dose of *Salmonella* Paratyphi A (challenge agent*)* to drink, which can cause this infection. The study will enroll groups of 3-5 participants at a time who complete the eligibility criteria. The dose of challenge agent will increase in each group to determine the exact dose needed to cause infection in humans. Participants receiving higher doses are more likely to develop infection.

Monitoring and Observation:

You will be admitted and administered the challenge dose of the infectious agent. You will stay in the hospital for 10-20 days . This is to ensure your safety, daily check-ups, including blood and stool samples, will help monitor your health and immune response. You will be required to take leave from work during this time. You will be provided with accommodation at the hospital along with three meals per day. No food or drinks from outside will be allowed to minimize the risk of other infections.

Table 2 Procedures and laboratory tests to be conducted during hospital stay for participants till they develop paratyphoid infection.

Written consent	Screening
Verbal continued consent	Daily
Medical history	Daily
Physical examination	At paratyphoid diagnosis
Vital signs	Daily
Urine pregnancy test	Screening, Day 0 (pre-challenge), PD/D14, D28 follow-up

Urine sample	Screening
Stool sample	Daily stool sample collection during hospital stay. On day 28, day 90, day 180 follow up Stool samples will also be collected 1 week after completion of antibiotic course, until 3 successive stool samples at least 24 hours apart are culture negative for S. Paratyphi A (clearance samples) Stool samples collected on specific time points will also be used for microbiome testing.
Blood sample	1. Daily blood sample collection for blood culture during hospital stay. Blood culture sample will be collected by trained study phlebotomist. 10-15 ml blood will be drawn and transferred to aerobic blood culture bottles. 2. Alternate day blood sample collection (3-4ml) for CBC during hospital stay and on day 28, day 90, day 180 follow up. 3. Alternate day blood sample collection (4-5ml) for CRP, Urea, Creatinine, electrolytes (serum Sodium and Potassium), and Liver function tests during hospital stay and on day 28, day 90, day 180 follow up. 4. Total blood volume taken will not exceed that of two blood donations over 180 days 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).
Saliva sample	1. Day 0 (pre-challenge) 2. Day 14 3. Paratyphoid diagnosis +12hrs 4. Day 90 and Day 180 follow-up (this will only be collected in a subset of participants)
Mood assessment	1. Day 0 (pre-challenge) 2. Day 14 3. At paratyphoid infection diagnosis

Paratyphoid Infection Diagnosis

Following administration of the challenge agent, paratyphoid infection may be diagnosed based on the following criteria:

1. **Positive Blood Culture**: Detection of *Salmonella* Paratyphi in a blood culture collected 72 hours post-challenge, using sterile technique by the study phlebotomist, regardless of symptoms.
2. **Fever Documentation**: Oral temperature exceeding 38°F recorded twice, at least 12 hours apart. Based on the above definition, once you are diagnosed, antibiotic treatment will begin immediately according to the study protocol and continue for 14 days.

The timeline for required sample collection after diagnosis is outlined in Table 3. Antibiotic treatment may also continue after your safe discharge from the hospital to ensure complete recovery.

Table 3 sample collection after Paratyphoid infection diagnoses

Investigation	Stool sample	Blood culture	Complete Blood count	CRP, U+Es, LFTs	Immunobiology samples	Saliva Samples (for a subset of participants)
PD	x	x	x	x	x	
PD +12hrs*	x	x	x	x	x	x
PD-1 (+24hrs*)	x	x	x	x	x	x
PD-2 (+48hrs)	x	x	x	x		x
PD-3 (+72hrs)	x	x	x	x		x
PD-4 (+96hrs)	x	x	x	x		x
PD-5 (+120hrs)	x	x	x	x	x	x
D14PD*	x	x	x	x		

*D14PD samples will be collected by either bringing the participant to AKU or via home visit by study team

Antibiotic Protocol

You will receive the appropriate antibiotics whether or not you develop a paratyphoid infection. If you are diagnosed with paratyphoid, treatment with antibiotics will begin immediately. If you do not develop the infection, antibiotics will start on day 14 after challenge. All participants will be admitted till at least day 10. Additionally you will need to stay in the hospital for 5 days after starting antibiotics and must be free of any symptoms before being discharge.

You will receive Ciprofloxacin for a total duration of 14 days. Ciprofloxacin has been proven effective in curing the infection caused by this strain, ensuring you receive proper treatment.

If your symptoms do not improve till day 5 of oral Ciprofloxacin, an adult Infectious Diseases specialist on the study team will assess your clinical condition and make a decision to start second or third line

antibiotics which will be Intravenous (IV) Ceftriaxone (second line) or oral Azithromycin or IV Meropenem (third line).

Visitation and Leave Guidelines

To minimize the risk of infection, strict movement and exposure restrictions will be in place for participants challenged with *Salmonella* Paratyphi A To protect both you and other vulnerable individuals—including children under 2 years old, the elderly, and immunocompromised individuals (e.g., those with uncontrolled diabetes, undergoing chemotherapy, or taking long-term steroids) - visits will not be permitted during the challenge phase and for five days after starting antibiotics.

Participants must adhere to strict isolation and infection control protocols and remain within designated premises.

Hospital Discharge Protocol

Participants will stay in the in-patient facility for 10–20 days and will be discharged based on the following criteria:

If Paratyphoid Infection is Diagnosed Before Day 14:

Once a paratyphoid infection is confirmed according to the specified criteria, you will begin a 14-day course of antibiotics. During the first five days of treatment, you will undergo close monitoring, including daily blood and stool cultures. After this period, you may be discharged if you are symptom-free and a blood culture taken 48 hours after initiating antibiotics is negative for *Salmonella* Paratyphi but not earlier than day 10

Discharge Timing:

You will be discharged from the hospital after completing at least 5 days of antibiotic treatment, provided that you are fever-free and your blood culture taken 48 hours after starting antibiotics show no growth of Salmonella Paratyphi. Additionally, discharge will not occur before Day 10 post-challenge, even if these conditions are met earlier.

These measures ensure the participant's safety while minimizing the risk of infection to others.

Treatment and Follow-Up:

If you develop paratyphoid infection you will receive antibiotic treatment immediately and will be followed according to the timeline and procedures mentioned in table 3. If you do not develop any signs of infection and blood culture is persistently negative, antibiotic treatment will commence on day 14 and will be continued for 14 days, you will be discharged home after 5 days of antibiotics (but not earlier than Day 10). In both cases, you will also attend follow-up visits for up to 6 months after the challenge to ensure complete recovery and gather further health data. The first follow up will be via phone call on day 21 post-challenge where a study nurse will

ask about your symptoms, general wellbeing and treatment compliance. These are followed by in-person visits with sample collection (table 5) on day 28, day 90 and day 180. For participants diagnosed with paratyphoid will have additional samples collected on PD D14 (table 3) for which the participant will either visit AKU or study team will visit home to collect those samples.

Table 4 Summary of sample collection for follow-up visits

Investigation	Urine pregnancy test	Stool sample	Full blood count	CRP, U+Es, LFTs	Saliva	Immunobiology samples
D28	x	x	x	x		x
D90		x	x	x	x	x
D180		x	x	x	x	x

What will happen to my samples?

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 7 years but may be longer if ethics committee agrees in AKU Bio-repository. The Oxford Vaccine Center Biobank is an ethically approved Biobank where your samples can be stored for an indefinite period of time if you provide your consent, which is optional.

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.

Convalescent carrier state

A convalescent (recovering) carrier state with paratyphoid is possible, it happens when the bacteria are still found in your stool even after you have been treated and recovered from the infection. If a stool culture is positive at any subsequent time point following the antibiotic treatment, you will be treated as a convalescent carrier. Ciprofloxacin, 500 mg will be taken orally twice a day for 7 days. After treatment 3 stool samples for culture will be taken to ensure clearance.

Potential Risks:

The strain of S. Paratyphi A administered in this challenge study is treated by commonly available antibiotics and has been used previously in multiple studies conducted by the University of Oxford in the United Kingdom. Keeping you in the hospital will ensure good and timely monitoring to ensure your safety so no risks or complications occur.

Risk of severe complications:

You may experience symptoms of paratyphoid fever, such as fever, headache, abdominal pain, and diarrhea which is to be expected. If Paratyphoid infection is not treated with appropriate antibiotics, severe complications such as bleeding from the gut, widespread infection (disseminated infection) or sepsis can occur. However, these severe complications have never been seen in similar studies using the same challenge strain when treated with antibiotics.

Risk of transmission of *Salmonella* Paratyphi

Paratyphi can be shed in the stool of infected individuals for up to six weeks. During this time, there is a risk of transmission to others, particularly vulnerable groups such as immunocompromised individuals, young children, and people on steroids. To minimize the risk, individuals are advised to practice proper hygiene, including thorough handwashing and maintaining sanitation after using the toilet, especially when handling food. These precautions should be followed until a stool culture confirms the absence of *Salmonella* Paratyphi, especially if it was previously detected. If a stool culture is positive at any subsequent time point following the antibiotic treatment, you will be treated as a convalescent carrier with antibiotics.

Blood Draws:

Blood draws may cause mild discomfort, bruising, or, rarely, infection.

Side Effects of Antibiotics:

If antibiotics are administered, you may experience side effects such as nausea or diarrhea. Other than rare instances of hypersensitivity to a drug, adverse effects are mild and manageable.

Benefits and Compensation

There are no direct benefits to you from participating in this study. However, your participation will contribute to research that may help prevent and treat paratyphoid fever in the future. You will be compensated for your time away from work or any inconvenience.

Confidentiality

All data collected will be kept confidential and stored securely. Your personal information will not be shared in publications or presentations. Anonymized data will be used for analysis and may be shared with other researchers.

Voluntary Participation and Right to Withdraw

Your participation is entirely voluntary. You can withdraw from the study at any time without penalty or loss of benefits. If you choose to withdraw, you will continue to receive appropriate medical care if needed. If you withdraw after the challenge has been administered, you will be required to take 14-day course of antibiotics.

If you agree to participate in this study and sign the consent form, you will receive a copy of the form for your records, while the original will be retained by the study team at the study site.

Contact Information

If you have questions about this study, please contact the Principal Investigator, Dr Farah Naz Qamar

at +92 21 3486 5035 or +92 21 3486 9674

Email at: farah.qamar@aku.edu, saba.anwer@aku.edu

Participant's Name:

Participant's Signature

Date:

Impartial Witness
I attest that:

- the information in the consent form and any other written information was accurately explained to and apparently understood by the participant or the participant's legally authorized representative and,
- informed consent was freely given by the participant or participant's legally authorized representative

Witness signature
Date

Investigator's Name:
Investigator's Signature:
Date:

Consent questionnaire

Section 1: Study Procedures	If you agree, please INITIAL box:
1. I confirm that I have read and understood the participant information sheet Version: ..... Dated…….. for this study. I have had the opportunity to consider the information, ask questions and have had these answers satisfactorily.	
2. I have received detailed information about the treatment schedule and potential side effects and have discussed any potential questions.	
3. I agree to remain at Aga Khan University from the time of challenge agent administration until I have completed at least 5 days of antibiotic treatment or 10 days post-challenge, whichever is longer. I will only be discharged if I am fever-free and my blood culture is negative for *Salmonella* Paratyphi.	
4. I understand that my participation is voluntary and that I'm free to withdraw at any time without giving any reasons, without my medical care or legal rights being affected.	
5. Should I wish to withdraw after I have been challenged with *Salmonella* Paratyphi A, I understand that I must take a course of antibiotics and will be asked to attend for further visits for safety reasons.	
6. I understand that should I fail to return for review or to take the full course of antibiotics I may become seriously ill and could even die.	
7. I will bring the 24-hour contact reply slip to the first study visit, signed by my 24-hour contact. I agree that the study team may contact this person if I cannot be contacted during the study.	
8. I agree to refrain from donating blood for the duration of the study.	

9. I understand that relevant sections of my medical notes and data collected during the study including identifiable information may be looked at by individuals from Aga Khan University research team and authorised representatives appointed by the Sponsor (Aga Khan University , where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	

10. I understand that data collected during the study may be shared with the study funder (Wellcome Trust) as needed for potential future licensing of a paratyphoid vaccine.	
11. I understand and agree that the study data, including identifiable information, will be held securely on a server at the Aga Khan University	
Section 2: Research Samples	
12. I agree to donate saliva, blood and stool samples for the purpose of this study to the Aga Khan University and I understand I will not gain any direct personal or financial benefit from them.	
13. I understand that my data and biological samples may be sent and stored within and outside of Pakistan for analysis by collaborating research groups and laboratories as described in the participant information sheet.	
13. I agree to have blood tests as part of this study, including testing for HIV, Hepatitis B and Hepatitis C.	
15. I understand and agree that my samples will be used in research aimed at understanding the genetic influences of response to infection with the bacteria that causes paratyphoid A disease and the effect of antibiotics on my gut bacteria. The results of these investigations are unlikely to have any implications for me personally.	
Section 3: Additional:	
16. I understand I should not have close contacts individuals who are immunocompromised (including pregnancy) or young children (under 2 years or attending pre-school or nursery) during in hospital stay.	

Section 4: SUMMARY		
17. I agree to take part in this study.		
Section 5: ***OPTIONAL (please INITIAL box yes or no accordingly):***		
	Yes	No

18. I agree to be contacted about other ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.		
19. I agree for my samples to be used, in a form that does not identify me, in future research here or abroad, which has ethics approval. I understand this research may involve commercial organisations.		
20. I agree my samples may be stored long-term in Pakistan for future research (which could include genetic testing).	Yes	No
21. I agree my blood samples may be stored long-term in the United Kingdom for future research (which could include genetic testing).	Yes	No

_____	_____	
Name of Participant	*Date (DD/MMM/YYYY)*	*Signature*
_____	_____	
Name of Person taking Consent	*Date (DD/MMM/YYYY)*	*Signature*