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Salmonella vaccine study in Oxford

Submission date
08/02/2022

Recruitment status
No longer recruiting

Registration date
29/04/2022

Overall study status
Completed

Last Edited
07/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol

Background and study aims
Nontyphoidal Salmonellae are bacteria that can cause gut infections resulting in diarrhoea, both in the UK and globally. However, under some circumstances, these bacteria can cause a more severe illness where the infection spreads beyond the gut into the bloodstream, a condition termed invasive non-typhoidal Salmonellosis (iNTS). iNTS disease is an under-recognised cause of disease and death in Sub Saharan Africa. In these regions, it primarily occurs in young children, particularly those with malaria and malnutrition. High death rates, difficulties in diagnosing this infection in the developing world, increasing resistance of the bacteria to common antibiotics, and spread via contaminated food and water make the development of an effective and affordable vaccine against iNTS an essential control measure.
A new and innovative vaccine (iNTS-GMMA) has been developed which is based on the formation of bacterial outer surface particles. This vaccine facilitates exposure of components of the bacteria to the human immune system without the risk of causing infection. Developed by GSK Biologicals and GSK Vaccines Institute for Global health (GVGH), the aim of this vaccine is to confer immune protection to the most common African strains of the bacteria causing iNTS disease.

Who can participate?
Healthy volunteers aged between 18 and 55 years

What does the study involve?
Participants will be randomly allocated to receive either iNTS-GMMA or a placebo (dummy vaccine). The safety and the immune response to the iNTS-GMMA vaccine are measured.

What are the possible benefits and risks of participating?
There are no specific benefits of taking part in this study. However, volunteers would be taking part in the knowledge that they have played a part in the early stages of developing a new vaccine against a bacteria that causes a significant burden of death and disease, particularly in sub-Saharan Africa and in children under 5 years of age for which there is currently no licensed vaccine.
Intra-muscular vaccination commonly causes a transient and self-limiting local inflammatory reaction. This may typically include discomfort, redness and swelling, and some volunteers may feel generally unwell in themselves for a short time. Anaphylaxis is a rare but a potentially life-threatening allergic reaction and may occur (very rarely) after immunisation. All clinical staff are

trained in the immediate treatment of anaphylactic reactions including the use of intramuscular adrenaline. Participants will be monitored for at least 1 hour after each vaccine dose is given. This study is the first time that iNTS-GMMA vaccine will be given to human participants, therefore it is not known for certain how participants will react to the vaccine. The pre-clinical studies of the vaccine have shown good safety results. In addition, GMMA-based vaccines against other bacteria have been safely used in over 100 people. However, this is a new vaccine and there may be side effects that are not currently known. The safety of the participants in all groups will be monitored following vaccination. This will be done by reviewing symptoms at visits and through the electronic Diary (eDiary). Participants will receive a card with study contact information and are advised to keep this card with them at all times during the study. Other medical staff can then contact the study doctor or nurse if needed to ask about the vaccine or product the participant has received. Participants will have access to a study doctor 24 hours a day until the end of the study. The researchers will emphasise participants staying in regular contact with the team. Blood tests can be painful and sometimes leave bruising or temporary discomfort, but these all resolve in a very short period of time. Rarely fainting can occur. Oral fluid samples are collected with a mouth swab and do not cause any discomfort. Stool sample collection is opt-in only and is a straightforward procedure. For females, if they became pregnant during the study would need to be withdrawn and undergo regular follow up during their pregnancy. This is standard practice because there is no data on the safety of this vaccine in pregnancy. Female participants will undergo pregnancy tests at screen and each subsequent vaccine and are advised on contraception during the study period.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
February 2022 to October 2023

Who is funding the study?
Funding is from the European Union’s Horizon 2020 research and innovation programme funding the Vacc-iNTS project

Who is the main contact?
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Contact information

Type(s)
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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-000510-14

Integrated Research Application System (IRAS)
1005098

Protocol serial number
OVG2020/01

Study information

Scientific Title
A Phase I clinical study to determine the safety and immunogenicity of a novel GMMA vaccine against invasive non-typhoid salmonella

Acronym
SALVO

Study objectives
To determine the safety and tolerability between two dose levels:
1. A lower dose of the iNTS-GMMA vaccine (5.3 µg STmGMMA in OAg and 5.3 µg SEnGMMA in OAg, each adsorbed on 0.35 mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)
2. A full dose of the iNTS-GMMA vaccine (20 µg STmGMMA in OAg and 20 µg SEnGMMA in OAg, each adsorbed on 0.35 mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)

in healthy adults 18-55 years inclusive when given three doses of vaccine at 0, 2- and 6-month intervals

To investigate the immunogenicity at two dose levels:
1. A lower dose of the iNTS-GMMA vaccine (5.3 µg STmGMMA in OAg and 5.3 µg SEnGMMA in OAg, each adsorbed on 0.35 mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)
2. A full dose of the iNTS-GMMA vaccine (20 µg STmGMMA in OAg and 20 µg SEnGMMA in OAg, each adsorbed on 0.35 mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)
in healthy adults 18-55 years when given three doses of vaccine at 0, 2- and 6-month intervals

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/04/2022, South Central - Oxford A Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, UK; +44 (0)207 104 8290, +44 (0)207 104 8206, +44 (0)207 104 8061; oxforda.rec@hra.nhs.uk), ref: 22/SC/0059

Primary study design
Interventional

Study design
Randomized double-blind placebo-controlled trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Invasive non-typhoid salmonella

Interventions
This vaccine trial is a participant-observer blinded, randomised placebo-controlled study. Participants are allocated to groups 1, 2 and 3 sequentially. They are considered enrolled once they have received the first vaccination. The study will assess the safety and immunogenicity of the iNTS-GMMA Vaccine at two dose levels:
1. A lower dose of the iNTS-GMMA vaccine (5.3 µg STmGMMA in OAg and 5.3 µg SEnGMMA in OAg, each adsorbed on 0.35mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)
2. A full dose of the iNTS-GMMA vaccine (20 µg STmGMMA in OAg and 20 µg SEnGMMA in OAg, each adsorbed on 0.35mg AL3+ / dose in isotonic 20 mM phosphate buffered saline pH 6.5)
in healthy adults 18-55 years inclusive when given three doses of vaccine at 0, 2- and 6-month intervals.

Group 1 (participant-observer blind):
Lower dose 10.6 µg total OAg of iNTS-GMMA vaccine (three intramuscular administrations at D0, D56 and D168). This group will consist of six participants subdivided into three cohort pairs. Within each pair the two participants will be randomised 1:1 to receive the 10.6 µg total OAg of iNTS-GMMA vaccine or a placebo. If the Data and Safety Monitoring Committee (DSMC) require further safety data at this dose level a further six participants subdivided into three cohort pairs may be enrolled.

Group 2 (participant-observer blind):
Full dose 40 µg total OAg of iNTS-GMMA vaccine (three intramuscular administrations at D0, D56 and D168). This group will consist of six participants subdivided into three cohort pairs. Within each pair the two participants will be randomised 1:1 to receive the 40 µg total OAg of iNTS GMMA vaccine or a placebo. If the DSMC require further safety data at this dose level a further six participants subdivided into three cohort pairs may be enrolled.

Group 3 (participant-observer blind):
18 participants will be randomised 2:1 to receive three intramuscular administrations at D0, D56 and D168 of either iNTS GMMA vaccine (either lower dose or full dose, depending on the safety results of Group 1 and 2)

The total duration for each participant on the trial is 12 months.

An electronic randomisation list is generated by the trial statistician using computer software and uploaded onto a web-based randomisation module to randomise participants electronically.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
iNTS-GMMA vaccine

Primary outcome(s)
The recording and assessment of local and systemic adverse events (AE) following and up to 7 days after administration of each vaccine dose:
1. Tenderness and pain at the injection site
2. Induration
3. Redness
4. Swelling
5. Headache
6. Malaise
7. Myalgia
8. Nausea and/or vomiting
9. Diarrhoea
10. Abdominal pain
11. Anorexia
12. Arthralgia
13. Fatigue
14. Fever
15. Blood parameters (haematology/biochemistry)
Any unsolicited symptom(s) not listed above in addition to any other AE, serious adverse events (SAE) or serious unexpected serious adverse reactions (SUSAR) thought the trial.

Solicited Adverse Events will be captured using an e-diary from Day 0 up to and including 7 days (D6) after vaccination. All adverse events will be captured up to Day 28. This will be done via the e-diary for the first 7 days (D0 to D6) and via study visits and participant phone calls to the study team. AEs which have resulted in medical visits or medication will be captured from enrolment

throughout the trial up to the participant last visit. SAEs will be captured from enrolment throughout the trial up to the participant last visit.

All adverse events will be graded 1-5:
0: Absence or resolution of symptom
1: Awareness of symptom but tolerated, transient or mild discomfort, little or no medical intervention required
2: Discomfort enough to cause limitation of usual activity, some medical intervention or therapy required
3: Significant interference with daily activity
4: Emergency department visit or hospitalisation
5: Fatality

Key secondary outcome(s)
Immunological assays to study immune responses to vaccines, including:
1. Antibody concentration against serovar specific O antigens determined by enzyme-linked immunosorbent assay (ELISA) before and after each dose
2. Serum IgG antibody responses against OAg from S. typhimurium and S. enteritidis in samples from all subjects at each time point (D0, D7, D28, D56, D63, D84, D168, D175, D196, D350) will be analysed by ELISA. Test samples will be analysed at three dilutions and colour change compared with a standard curve made with calibrated human serum pool, included on each assay plate. Anti-OAg responses will be expressed in ELISA units. Plate coating antigens are well characterized OAg purified by GVGH. The analysis will be completed a maximum 8 months after the last participant last visit.

Completion date
18/10/2023

Eligibility

Key inclusion criteria
1. Willing and able to give informed consent for participation in the study
2. Aged between 18 and 55 years inclusive
3. In good health as determined by:
3.1. Medical history
3.2. Physical examination
3.3. Clinical judgment of the investigators
4. (Females) Willing to use effective contraception (such as the oral contraceptive pill, contraceptive implant or barrier methods) from 1 month prior to receiving the first vaccine and for the duration of the study
5. Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of diary cards
6. Willing to allow his or her General Practitioner and/or Consultant, if appropriate, to be notified of participation in the study
7. Willing to allow the study team access to medical records for the purposes of eligibility assessment and/or safety follow up during the trial.
8. Willing to provide their national insurance number or passport number to be registered on The Over-Volunteering Prevention System (TOPS)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
30

Key exclusion criteria
Current exclusion criteria as of 14/09/2022:

The participant may not enter the study if any of the following apply:
1. History of significant organ/system disease that could interfere with the trial conduct or completion in the clinical judgement of the investigators. This includes any history of significant disease in the following:
1.2. Cardiovascular disease including congenital heart disease, previous myocardial infarction, valvular heart disease (or history of rheumatic fever), previous bacterial endocarditis, history of cardiac surgery (including pacemaker insertion), personal or family history of cardiomyopathy or sudden adult death
1.3. Respiratory disease such as uncontrolled asthma and chronic obstructive pulmonary disease
1.4. Endocrine disorders such as diabetes mellitus and Addison's disease
1.5. Significant renal or bladder disease
1.6. Biliary tract disease
1.7. Gastro-intestinal disease such as inflammatory bowel disease, abdominal surgery within the last two years, coeliac disease and liver disease (including hepatitis B or C infection)
1.8. Neurological disease such as seizures and myasthenia gravis
1.9. Haematological disease including coagulation problems
1.10. Metabolic disease such as glucose-6-phosphate dehydrogenase deficiency
1.11. Psychiatric illness requiring hospitalisation
1.12. Depression, anxiety or other psychiatric illness whose severity is deemed clinically significant by the study investigators
1.13. Known or suspected drug and/or alcohol misuse (alcohol misuse defined as an intake exceeding 42 units per week)
1.14. Non-benign cancer, except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ
2. Have any known or suspected impairment or alteration of immune function, resulting from, for example:
2.1. Congenital or acquired immunodeficiency (including IgA deficiency)
2.2. Human Immunodeficiency Virus infection or symptoms/signs suggestive of an HIV-associated condition
2.3. Autoimmune disease
2.4. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic

corticosteroid therapy (including for more than 7 days consecutively within the previous 3 months).
3. Study significant abnormalities on screening investigations, that are either unlikely to resolve or do not resolve on repeat testing (at the discretion of an Investigator) within the recruitment timeline of the study
4. Have received any oral typhoid vaccination (e.g. Ty21a or M01ZH09) within the last 3 years or a paratyphoid vaccine (as part of a clinical trial)
5. Have participated in previous typhoid or paratyphoid challenge studies (with ingestion of challenge agent).
6. Receipt of a live vaccine within 4 weeks prior to vaccination or a killed vaccine within 7 days prior to vaccination
7. Plan to receive any vaccine other than the study vaccine within 4 weeks after any study vaccination (COVID-19 vaccine exempt, see Section 9.14)
8. Any history of allergy or anaphylaxis to a previous vaccine or vaccine component
9. Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
10. Participation in another research study involving an investigational product or that which may compromise the integrity of the study (e.g. significant volumes of blood already taken in previous study) in the past 12 weeks, or are planning to do so within the trial period
11. Planned donation of blood/blood products outside of the study and during the trial period
12. Inability, in the opinion of the Investigator, to comply with all study requirements including likelihood of successful venepuncture during the trial
13. Female participants who are pregnant, breastfeeding/lactating or planning pregnancy during the course of the study
14. Weight less than 50kg or a BMI < 18.4 kg/m2 or a BMI > 40 kg/m2
15. Any other significant disease or disorder which, in the opinion of the Investigator, may:
15.1. Put the participants at risk because of participation in the study
15.2. Influence the result of the study
15.3 Impair the participant's ability to participate in the study

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Previous exclusion criteria:

1. History of significant organ/system disease that could interfere with the trial conduct or completion in the clinical judgement of the investigators. This includes any history of significant disease in the following:
1.1. Cardiovascular disease including congenital heart disease, previous myocardial infarction, valvular heart disease (or history of rheumatic fever), previous bacterial endocarditis, history of cardiac surgery (including pacemaker insertion), personal or family history of cardiomyopathy or sudden adult death
1.2. Respiratory disease such as uncontrolled asthma and chronic obstructive pulmonary disease
1.3. Endocrine disorders such as diabetes mellitus and Addison's disease
1.4. Significant renal or bladder disease
1.5. Biliary tract disease
1.6. Gastro-intestinal disease such as inflammatory bowel disease, abdominal surgery within the last two years, coeliac disease and liver disease (including hepatitis B or C infection)
1.7. Neurological disease such as seizures and myasthenia gravis
1.8. Haematological disease including coagulation problems
1.9. Metabolic disease such as glucose-6-phosphate dehydrogenase deficiency
1.10. Psychiatric illness requiring hospitalisation
1.11. Depression, anxiety or other psychiatric illness whose severity is deemed clinically significant by the study investigators

1.12. Known or suspected drug and/or alcohol misuse (alcohol misuse defined as an intake exceeding 42 units per week)
1.13. Non-benign cancer, except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ
2. Have any known or suspected impairment or alteration of immune function, resulting from, for example:
2.1. Congenital or acquired immunodeficiency (including IgA deficiency)
2.2. Human Immunodeficiency Virus (HIV) infection or symptoms/signs suggestive of an HIV-associated condition
2.3. Autoimmune disease
2.4. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic corticosteroid therapy (including for more than 7 days consecutively within the previous 3 months).
3. Study significant abnormalities on screening investigations, that are either unlikely to resolve or do not resolve on repeat testing (at the discretion of an Investigator) within the recruitment timeline of the study
4. Prior history of receipt of a typhoid vaccine (e.g. Ty21a, M01ZH09) or a paratyphoid vaccine (as part of a clinical trial)
5. Prior history of participation in a Typhoid or Paratyphoid controlled human infection study
6. Receipt of a live vaccine within 4 weeks prior to vaccination or a killed vaccine within 7 days prior to vaccination
7. Plan to receive any vaccine other than the study vaccine within 4 weeks after any study vaccination (COVID-19 vaccine exempt, see Section 9.14)
8. Any history of allergy or anaphylaxis to a previous vaccine or vaccine component
9. Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
10. Participation in another research study involving an investigational product or that which may compromise the integrity of the study (e.g. significant volumes of blood already taken in the previous study) in the past 12 weeks, or are planning to do so within the trial period
11. Planned donation of blood/blood products outside of the study and during the trial period.
12. Inability, in the opinion of the Investigator, to comply with all study requirements including the likelihood of successful venepuncture during the trial
13. Female participants who are pregnant, breastfeeding/lactating or planning pregnancy during the course of the study
14. Weight less than 50 kg or a BMI < 18.4 kg/m² or a BMI > 40 kg/m²
15. Any other significant disease or disorder which, in the opinion of the Investigator, may:
15.1. Put the participants at risk because of participation in the study
15.2. Influence the result of the study
15.3. Impair the participant's ability to participate in the study

TEMPORARY EXCLUSION CRITERIA (Please see protocol for further details).

Date of first enrolment
05/05/2022

Date of final enrolment
24/11/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Vaccine Group
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			24/01/2025	No	No
Dataset			26/11/2024	No	No
Dataset		14/01/2025	21/01/2025	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 3.0	14/06/2022	14/09/2022	No	No
Protocol file	version 3.1	13/01/2023	19/01/2023	No	No