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A study to test the safety and immune response in adult humans of a new vaccine against four different types of Shigella bacteria

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01/04/2023

Recruitment status
Stopped

Registration date
06/09/2023

Overall study status
Stopped

Last Edited
01/03/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Shigella is a group of bacteria which are well known to cause food poisoning throughout the world. In certain circumstances they can cause severe bloody diarrhoea (dysentery), known as shigellosis, and less often can spread beyond the gut leading to blood poisoning, in some cases causing severe illness and death. This is of particular concern in individuals with a weaker immune system. Shigella bacteria are transmitted through contaminated food or water supplies or from person to person through direct contact with hands or surfaces. Shigella bacteria cause around 200,000 deaths per year, with 60,000 of these in children under 5 years old, and are a particular problem in southern Africa and Asia.

In this study we are investigating a new vaccine against Shigella called the Shigella4V vaccine. This vaccine has been developed by a pharmaceutical company called LimmaTech Biologics AG, based in Switzerland, with which the Oxford Vaccine Group is collaborating on this study.

Shigella4V vaccine contains small particles of structures present on the outer surface of the four most common types of Shigella bacteria that cause shigellosis (Shigella flexneri 2a, 3a, 6 and S. sonnei). These particles are collectively known as “O-antigens”. The vaccine also contains a protein from another type of bacteria called “Exoprotein A” (EPA) that helps to stimulate the immune system. The vaccine does not contain Shigella bacteria and therefore cannot cause infection or disease.

It is expected that these O-antigen particles will stimulate the immune system to produce a protective response against shigellosis and thus prevent dysentery and sepsis. The O-antigen and EPA particles are diluted in Alhydrogel, a common vaccine component designed to improve the immune system’s response.

The study is being conducted to evaluate the safety of the vaccine and how well it stimulates the immune system against Shigella bacteria. In addition, the study will use antibodies against the O-

antigen collected from participants' blood tests to create an international reference standard, which can be used to develop laboratory tests and compare how well this vaccine or future vaccines against Shigella are working in the individuals being vaccinated.

Who can participate?
The study will recruit healthy adults aged 18 to 55 years old who will first have a screening visit to confirm suitability for the trial.

What does the study involve?
In this study everyone will receive the active vaccine, but some participants will receive a low dose (half dose) and some the full dose. This is so that we can study whether different doses have different effects on the immune system, and whether they cause different side-effects. Participants aged between 18 to 55 years will be enrolled sequentially into one of two groups to receive either the half dose (the first 20 participants) or full dose vaccine (the next 20 participants).

Each participant would receive 1 vaccination with the Shigella4V vaccine. In addition, each participant would require blood tests immediately before their vaccination and at specific intervals after vaccination. As well as a screening visit, the study will require a total of 4 visits over a 6-month period (the vaccination visit, then at 1 week, 1 month and 6 months after vaccination). A larger blood sample (435ml) will be taken at the visit 1 month after the vaccination which will be used to create the international reference standard.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
In general, the risks are in relation to the vaccine and blood sampling.
General: intra-muscular vaccination can commonly cause reactions, although most tend to be minor and only last a few days. These may typically include discomfort, redness and swelling at the injection site. As for all vaccines some volunteers occasionally may feel generally unwell, develop fevers, muscle aches, joint aches, headache, experience loss of appetite, nausea / vomiting, abdominal pain or diarrhoea. Not everyone will experience symptoms and if they do occur, they should resolve after a few days.
Anaphylaxis is a very rare but a potentially life-threatening allergic reaction and may occur after vaccination. All clinical staff are trained in the immediate treatment of anaphylactic reactions including the use of intra-muscular adrenaline. It is for this reason you need to wait at least 30 minutes after each vaccine dose is given, as this would be within the typical time frame should this reaction occur.
Shigella4V vaccine: the studies performed in animals and in human trials of both the Shigella4V vaccine and the similar Flexyn2a vaccine have shown good safety results. These vaccines were found to be well-tolerated and safe in the volunteers who received them. Nevertheless, this is a new vaccine and there may be side effects we do not know about. It is important for participants to be aware of this. However, we have multiple measures in place to ensure participant safety during the trial as outlined below.
Throughout the study, the safety of the participants in all groups will be monitored following vaccination. This will be done by reviewing of symptoms at visits and through the electronic Diary (eDiary). For participant safety there will be a local Safety Committee who will periodically monitor the overall safety of the trial. In addition, participants will be provided with study team contact details who are available 24/7 should a participant need to contact the study team. Participants will be asked to provide contact details of a person who would act as a second contact, only to be used in an emergency or when needing to contact a participant urgently.

Blood sampling
Blood tests can be painful and sometimes leave bruising and/or temporary discomfort, but these all resolve in a very short period of time. Rarely fainting can occur. As part of this study we will take a single large volume blood sample (400ml), which can lead to feelings of light-headedness, dizziness or weakness. The purpose of this sample is to create a supply of antibodies directed towards the Shigella bacteria O-antigen that can be used as a reference standard to develop laboratory tests and compare how well this vaccine or future vaccines are working in the individuals being vaccinated.

Pregnancy
For females, if a female participant became pregnant during the study she would need to be withdrawn and we would regularly follow up with her during her pregnancy until delivery. This is standard practice because there is no data on the safety of this vaccine in pregnancy. Female participants will undergo pregnancy tests at the screening visit and vaccination visit. Female participants of childbearing potential must be willing to ensure that they use highly effective contraception during the trial.

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

When is the study starting and how long is it expected to run for?
March 2023 to December 2024

Who is funding the study?
Bill & Melinda Gates Foundation (USA)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2023-000129-10

Integrated Research Application System (IRAS)
1007321

Central Portfolio Management System (CPMS)
55912

Protocol serial number
OVG2023/01

Study information

Scientific Title
Safety and Immunogenicity of a Shigella tetravalent bioconjugate vaccine in adults

Acronym
SIS4V study

Study objectives
Primary objectives:
1. To assess the safety, tolerability and reactogenicity of the Shigella4V candidate vaccine in healthy adults aged 18-55 years at two dose levels
2. To assess immunogenicity of the two different doses and establish an International Standard for anti-Shigella serum (human).

Exploratory objective:
Exploratory immunology to look at the level of serum IgG against the 4 Shigella vaccine-serotypes at additional timepoints following vaccination and the changing features of the participant immune response including innate, antibody and cell-mediated responses from vaccination to 6-months post-vaccination

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 01/09/2023, South Central - Berkshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8178; Berkshire.rec@hra.nhs.uk), ref: 23/SC/0130

Primary study design
Interventional

Study design
Interventional non randomized

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Vaccination designed to prevent infection with Shigella bacterial species (Shigella flexneri 2a, 3a, 6 and S. sonnei) and risk of shigellosis, sepsis and death.

Interventions
The study will recruit healthy adults aged 18 to 55 years old who will first have a screening visit to confirm suitability for the trial. On enrolment, participants will be enrolled into 1 of 2 groups to receive either the half dose or full dose of the vaccine. The vaccine is LimmaTech Shigella bioconjugate 4-valent vaccine (Shigella4V). A half dose is 24 µg O-antigen (6 µg for each component) and a full dose is 48 µg O-antigen (12 µg for each component). The vaccine is administered by intramuscular injection. Each participant would receive one vaccination with the Shigella4V vaccine. In addition, each participant would require blood tests immediately before each vaccination and at specific intervals after vaccination. The study will require a total of four visits and one telephone call over a six month period (vaccination visit, one week, one month, three months (telephone call only) and six months after vaccination). A larger blood sample (400ml) will be taken at the 1 month visit. This blood sample will be used to create an International Standard for anti-Shigella serum (human).
The study is open label, there is no randomisation.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
Shigella4V [Sf2E (proposed), Sf3E (proposed), Sf6E (proposed), SsE (proposed), Aluminium hydroxide]

Primary outcome(s)
1. Assess the safety, tolerability and reactogenicity of the Shigella4V candidate vaccine:
1.1. The recording and assessment of local and systemic adverse events following administration of the vaccine.
1.2. Any other medically attended Adverse Event , Serious Adverse Event or Suspected Unexpected Serious Adverse Reaction starting from date of vaccination (D0) and for the following one hundred and sixty eight days (D168)
2. Assess immunogenicity of two different bioconjugate doses and establish an International Standard for anti-Shigella serum (human):
Level of serum IgG against the 4 Shigella vaccine-serotypes will be tested by ELISA or similar assays, pre and post vaccination, in the two arms. International serum standard will be generated using ELISA methods on 400ml of blood per participant. The standard will be assigned a value for anti-S. flexneri 2a, anti-S. flexneri 3a, anti-S. flexneri 6 and anti-S. sonnei based on reactivity to the relevant LPS O-antigens in immunoassays. Values for IgG and IgA will be assigned to the International Standard

Key secondary outcome(s)
Exploratory immunology to look at the level of serum IgG against the 4 Shigella vaccine-serotypes at additional timepoints following vaccination and the changing features of the participant immune response including innate, antibody and cell-mediated responses from vaccination to 6-months post-vaccination. Adaptive, innate, humoral, cell-mediated and mucosal responses to vaccination at baseline and post-vaccination time points, D0, D7, D28 and D168 using immunological laboratory assays

Completion date
31/12/2024

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
1. Willing and able to give informed consent for participation in the trial.
2. Male or Female, aged 18-55 years inclusive at time of vaccination.
3. In good health as determined by medical history, physical examination and clinical judgment of the study team.
4. Female participants of childbearing potential must be willing to ensure that they use highly effective contraception during the trial
5. In the Investigator’s opinion, is able and willing to comply with all trial requirements.
6. Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of diaries
7. Willing to provide their national insurance number or passport number to be registered on

The Over-Volunteering Prevention System (TOPS).
8. Agree to allow study staff to access the participant's NHS health records, vaccination records and medical history as required for study purposes and to allow his or her GP (and/or Consultant if appropriate), to be notified of participation in the study.
9. Agree to refrain from donating blood for the duration of the study.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Key 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. 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 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 participated in previous Shigella species vaccination study
5. Receipt of a live or live attenuated vaccine within 4 weeks prior to vaccination or inactivated vaccine within 7 days prior to vaccination, or receipt of any vaccine other than the study vaccine within 4 weeks after any study vaccination.
6. Any history of allergy or anaphylaxis to a previous vaccine or vaccine component
7. Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
8. 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
9. Planned donation of blood/blood products outside of the study and during the trial period.
10. Inability, in the opinion of the Investigator, to comply with all study requirements including likelihood of successful venepuncture during the trial
11. Female participants who are pregnant, breastfeeding/lactating or planning pregnancy during the course of the study
12. Weight less than 50kg or a BMI < 18.4 kg/m² or a BMI > 40 kg/m²
13. Any other significant disease or disorder which, in the opinion of the Investigator, may:
13.1. Put the participant at risk because of participation in the study
13.2. Influence the result of the study
13.3. Impair the participant's ability to participate in the study

Date of first enrolment
01/03/2024

Date of final enrolment
31/05/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Vaccine Group
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Sponsor information

Organisation
LimmaTech Biologics AG

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
De-identified participant data will be made available upon requests directed to the chief investigator. Proposals will be reviewed and approved by the sponsor and chief investigator on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

IPD sharing plan summary
Available on request