ISRCTN22467293 https://doi.org/10.1186/ISRCTN22467293

Streptococcus pneumoniae nasopharyngeal experimental carriage study of attenuated strains to assess whether reducing the ability of this bacteria to cause illness can assist in improving immunity

Submission date
24/09/2018

Recruitment status
No longer recruiting

Registration date
27/09/2018

Overall study status
Completed

Last Edited
09/10/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Streptococcus pneumoniae bacteria is the most common cause of pneumonia. The presence of this bacteria in the nose/throat stimulates the body's immune system and can prevent future colonisation that could lead to illness when we are vulnerable. The live bacteria can be altered to make it safer to administer by removing the genes linked to infection. Current vaccines given to adults do not use live bacteria and are not effective at preventing lung infections. The aim of this study is to determine whether pneumococcal lung infections linked to pneumonia could be prevented by spraying the nose of healthy volunteers with live pneumococcal bacteria to boost the immune system.

Who can participate?
Healthy volunteers aged 18 – 50

What does the study involve?
Participants are randomly allocated to one of four groups to compare two types of genetically altered bacteria with two control groups: i) the normal pneumococcus bacteria naturally found in healthy people, and ii) a saline (salt water) control group. Samples are collected, for example nasal wash fluid and blood, to assess the immune response and presence of the bacteria. After about six months the researchers monitor whether their immune response prevents the naturally found bacteria from being carried in the nose.

What are the possible benefits and risks of participating?
In future these data may contribute to the development of a live vaccine in particular for higher risk groups including adults aged over 65 or with respiratory (lung) conditions. Over the last nine years eleven studies of this bacteria have been conducted in healthy volunteers in Liverpool. Over 1000 healthy adults have taken part in studies where the naturally found bacteria were put

in their nose safely with no serious side effects. There is a very small risk of infection to participants or their close contacts. A safety leaflet explains what to do if they feel unwell or have symptoms, and a thermometer is provided. The researchers check that participants are at a low risk of infection then monitor them closely. Antibiotics are provided to treat symptoms without delay if required. Participants are advised not to become pregnant during the study and to tell the research team if they do. The only side effect of nasal wash is a little discomfort and some experience a runny nose. Sampling nasal cells can cause a little discomfort, a spot of blood from the scratch, or may trigger a response to briefly make your eyes water. Sampling nasal fluid causes little if any discomfort. Some people can feel light-headed when giving a blood sample and sometimes they may have a bruise.

Where is the study run from?
1. Liverpool School of Tropical Medicine (UK)
2. Royal Liverpool and Broadgreen Hospital (UK)

When is the study starting and how long is it expected to run for?
June 2018 to June 2020

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Helen Hill
Helen.hill@lstmed.ac.uk

Study website
http://www.lstmed.ac.uk/research/topics/pneumonia

Contact information

Type(s)
Scientific

Contact name
Dr Helen Hill

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
39034

Study information

Scientific Title
Experimental Human Pneumococcal Challenge (EHPC) Model: Streptococcus pneumoniae Nasopharyngeal Experimental carriage study of Attenuated Strains (SNEAS) – proof of concept in healthy adults: working towards vaccines for pneumonia, a single-blind randomised controlled trial

Acronym
SNEAS

Study objectives
Hypotheses: Intranasal administration of live attenuated S. pneumoniae to humans improves mucosal immunity and prevents colonisation with wild type S. pneumoniae (associated with pneumonia in vulnerable groups).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Liverpool East Research Ethics Committee, 03/09/2018, ref: 18/NW/0481

Study design
Randomised; Interventional; Design type: Prevention, Other

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Streptococcus pneumoniae infection

Interventions

A single blind randomised controlled trial design allows an unbiased methods for comparison of four groups comparing S. pneumoniae i) attenuated strain I, ii) attenuated strain, II iii) wild type bacteria (control), and v) saline (control). The laboratory team are blinded for Stage II at the time of assessing carriage as the detection of the wild type S. pneumoniae in nasal washes is the primary outcome. As such there is no need to blind the participant or clinical team.

Justification of control: this provides a comparison of symptoms for example that may be influenced by seasonal changes over the period of the study.

Clinical visits will take place in the dedicated research facility: Accelerator Research Clinic in the Liverpool School of Tropical Medicine.

This is an adaptive trial design with an interim analysis. In the event that one strain does not show either carriage or immune response then the TSC will determine whether to replace this rather than continue with a strain that is unlikely to be effective as a potential vaccine. The strain is attenuated with the intention of making it safer by removing genes associated with illness. Pre-clinical data in mice suggests this strain will stimulate an immune response and this research will evaluate whether this translates to humans.

Procedures to reduce bias: the trial will be single blind achieved by blinding the laboratory staff who assess the primary outcome in stage II. Participants are randomised to one of four arms including two control arms.

Recruitment: The target is to complete 108 participants, up to 150 may be screened to achieve this as we anticipate 1: 10 will already have pneumococcus in their nose 'natural carriers' (it is commonly found in the nose of healthy adults and more common in children). Also, a higher drop out rate than in previous studies is anticipated due to the 6-month interval between stage I and II.

Group size calculations using two-tailed T tests and 80% power (5% statistical significance) show that to detect a reduction in the proportion of subjects colonised from 50% for the negative control group to 15% on challenge for the attenuated strain groups needs 27 completed subjects per group. To allow for drop out or to replace an arm due to futility the aim is to recruit up to a total of 150 subjects with no planned sex bias.

Healthy volunteers will be identified consistent with the EHPC previous studies:
1. Local public areas or events such as freshers fairs
2. Physical notice boards, table displays and other public display areas
3. Electronic notice boards
4. The intranet/internet of local universities, colleges, LSTM and RLBUHT
5. Social media including Facebook and Twitter
6. Local press, television and radio
7. RLBUHT Consent for Consent Database
8. Electoral roll, mail leaflet with letter

Information may be sent to those who register their interst in research on the C4C data base at Royal Liverpool Hospital.

Potential participants will be given a participant information sheet, invited to attend a short presentation then be invited to consent by a registered health professional. The consent process is consistent with GCP allowing volunteers to voluntarily participate who are eligible and have

the capacity to consent and inform the team of any health issues during the study. Consent will be taken by nursing and medical staff who are competent (trained in consent and the protocol) and delegated the role by the CI.

Participants will attend the following clinic visits:
Stage I: screening, randomisation then seven follow up visits.
Stage II: screening, inoculation with the wild type bacteria then three follow up visits

Screening: this health check will confirm their medical history, monitor vital signs, and baseline samples.

Sample schedule: on each visit samples include nasal wash (squirting 5ml of water into the nose then letting it drip out). Blood samples may be taken within the guidance of no more than 50 ml per visit or 185 ml per month recommended for research.

Following the interim analysis further samples may be added for example home samples (saliva and putting nasosorption paper in the nose) or have rhinoporbe samples (small scratch in the nose with a small probe (toothpick)).

Shedding: swabs of the hand may be taken to determine if bacteria move from the nose to the hand.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome measure
The efficacy of nasal administration of attenuated Streptococcus pneumoniae strains to induce mucosal immunity thereby prevent future colonisation with wild type Streptococcus pneumoniae using the Experimental Human Pneumococcal Challenge Model; Timepoint(s): Participants are challenged with the wild type 6B at six months post inoculation.

Secondary outcome measures
1. Antibodies and cellular adaptive immune responses local and systemic to S. pneumoniae pre and post colonisation
2. The presence, density and duration of pneumococcus measured using classical microbiological and qPCR techniques on nasal wash collected following inoculation on day, 2, 6, 16, 22, 27 or 36 and after challenge on day 2, 6 or 14
3. Sequencing and in vitro testing of bacteria recovered to ensure genome and phenotypic stability
4. Presence of S. pneumoniae in nasal wash following cultures when carriage positive at each study visit 2, 6, 16, 22, 27 or 36 and after challenge on day 2, 6 or 14
5. Presence of S. pneumoniae on hand swabs or culture plate following standard microbiology cultures when carriage positive at selected visits subject to carriage status

Overall study start date

01/06/2018

Completion date
30/06/2020

Eligibility

Key inclusion criteria
1. Healthy volunteers
2. Age 18 – 50 years
3. Capacity to give informed consent
4. Ability to speak fluent English

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 150; UK Sample Size: 150

Key exclusion criteria
1. Research participant currently involved in another study unless observational or non-interventional
2. Participant in a previous EHPC trial
3. Natural carriers of S. pneumoniae identified following initial screening*
4. Vaccination: pneumococcal vaccination (routine in UK babies born since 2005 or US 2001)
5. Allergic to penicillin, amoxicillin
6. Health history:
6.1. Chronic ill health including, immunosuppressive history, diabetes, asthma (on regular medication), recurrent otitis media or other respiratory disease
6.2. Medication that may affect the immune system or clotting e.g. steroids, inflammation altering (e.g. nasal steroids, roacutane or aspirin)
6.3. Recent antibiotics (within the last 4 weeks or long term for known active chronic infection)
6.4. Splenectomy
6.5. Current acute severe febrile illness
6.6. Major pneumococcal illness requiring hospitalization
6.7. Other conditions considered by the clinical team as a concern for participant safety or integrity of the study
7. Direct caring role or close contact with individuals at higher risk of infection:
7.1. Children under 5 years age
7.2. Chronic ill health or immunosuppressed adults
7.3. Adults over the age of 75 years

8. Smoker:
8.1. Current or ex-smoker in the last 6 months
8.2. Significant smoking history - more than 20 cigarettes per day for 10 years or the equivalent (> 10 pack years)
9. Women of child-bearing potential (WOCBP) who are:
9.1. Not deemed to have sufficient/effective birth control or confirmed abstinence
9.2. Pregnant
10. History of drug or alcohol abuse (at discretion of the clinician)
11. Overseas travel planned in follow up period (if unplanned contact team)

Date of first enrolment
01/10/2018

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Liverpool School of Tropical Medicine
Respiratory Research
Accelerator Building
Liverpool School of Tropical Medicine
1 Daulby Street
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United Kingdom
L7 8XZ

Study participating centre
Royal Liverpool and Broadgreen Hospital
Prescott Street
Liverpool
United Kingdom
L7 8XP

Sponsor information

Organisation
Liverpool School of Tropical Medicine

Sponsor details
c/o Carl Henry, Research and Governance Manager
Liverpool
United Kingdom
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Sponsor type
University/education

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/M011569/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/06/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Professor Daniella Ferreira (Daniella.Ferreira@lstmed.ac.uk). Summary datasets generated and/or will be included in the subsequent results publication. The data-

sharing plans for the current study will be made available at a later date. Participants consent on the understanding that their data will be anonymised if accessed by others not directly in the clinical team.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V2.0		27/09/2018	No	Yes
Results article		12/01/2021	07/01/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		09/08/2023	09/10/2024	Yes	No