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Developing better pneumococcal vaccines to cover important disease-causing strains: a healthy volunteer challenge study

Submission date
23/03/2022

Recruitment status
No longer recruiting

Registration date
04/04/2022

Overall study status
Completed

Last Edited
18/12/2024

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
A bacteria called pneumococcus is often found in the noses of healthy adults and children without causing any symptoms or disease. However, in some people, such as older age, chronically ill adults or very young children, it is more likely to cause illness. Mild infections with pneumococcus are very common, such as ear infections in children. Less frequently, the bacteria can infect the lung (causing pneumonia), the brain (causing meningitis) or the blood (causing sepsis). These more serious illnesses are very uncommon in healthy adults. It is thought that small numbers of this bacteria in the nose (nasal colonisation) may actually protect against pneumococcal disease such as pneumonia.
The experimental human pneumococcal challenge (EHPC) model is a way of putting drops of bacteria into the nose. Researchers have studied this model of putting bacteria in the nose safely in over 1500 volunteers over the past decade with no serious side effects. They now want to test the model using a different strain of the bacteria that is commonly found in the community, SPN3.
The aim of this study is to determine how much pneumococcus is needed to achieve nasal colonisation and how long the bacteria live in the nose for before natural immune responses eradicate them. By doing this, the researchers will then be able to test how well future vaccines prevent colonisation with pneumococcus. They also want to learn more about how the immune system responds to nasal colonisation with pneumococcus, again to help with the development of new vaccines.

Who can participate?
Healthy young adults aged 18-50 years (inclusive)

What does the study involve?
The study involves nine visits over a 4-5 week timescale. The samples that are taken at clinic visits consist of nasal washes, where the researchers gently squirt a little salty water into the nose and after a few seconds the water runs out into a sample bowl. This will tell the researchers about the bacteria in the nose and immune responses. The researchers will also take a small cotton swab and wipe the back of the throat in a circular motion. This is used to detect bacteria

and viruses in the throat. To collect cells from the nose, the researchers place a small piece of paper into each nostril for two minutes. They insert a very small plastic spoon (like a toothpick) to collect cells from inside the nose. They will perform this twice on each nostril. The researchers take a blood sample from a vein in the arm using a needle. They will take up to 80 ml (about the same as eight tablespoons) during a visit. The researchers will use gentle methods to find out if bacteria move from the nose to the hand, such as a swab of the participant's hand after rubbing the nose or coughing onto a plate that is used to grow bacteria.

What are the possible benefits and risks of participating?
The participant is reimbursed for each clinic visit to a maximum of £295.00 if all visits are completed. Due to inoculating participants with pneumococcus, there is a low risk of otitis media and sinusitis, and a very low risk of pneumonia, bacteraemia and meningitis. While the risk to individuals of developing any infection is very low, the study is designed to ensure any risk is minimal. In order to minimise this risk, participants who would be at risk of invasive pneumococcal disease will be excluded. Only healthy young adults will be eligible to participate. In the dose-ranging study, the initial dose of SPN3 will be initially tested in a small group of participants to ensure it is safe to use, before being tested in up to 10 participants. The selected serotypes of pneumococcus will be fully antibiotic sensitive.

Where is the study run from?
Accelerator Research Clinic (ARC) (UK)

When is the study starting and how long is it expected to run for?
November 2021 to November 2023

Who is funding the study?
Merck Sharp & Dohme (UK)

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
306700

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
22-003, IRAS 306700

Study information

Scientific Title
Serotype 3 experimental human pneumococcal challenge; dose-ranging and reproducibility in a healthy volunteer population

Acronym
Challenge 3

Study objectives

The LSTM Experimental Human Pneumococcal Challenge (EHPC) model allows vaccines to be tested for their effect on experimental colonisation, in a more cost-effective manner than phase III clinical trials, as far fewer participants are required. In the EHPC model, participants are intranasally inoculated with SPN and about half of them develop a stable colonisation episode for about 1-3 weeks at a typical density of natural colonisation. Host samples including nasopharyngeal washes, nasal cells and blood samples are taken to assess colonisation and duration as well as host immune responses. Over the years, the model has provided key insights into human immune mechanisms that are associated with protection and susceptibility to colonisation acquisition. The model is well developed for SPN6B and SPN15B with over 1500 challenged in 25 independent studies, showing the model is safe and has reproducible attack rates. More recently researchers have challenged 96 participants with three different SPN3 strains (manuscript in preparation; strains are proprietary to a third party) in a series of different doses. Colonisation attack rates varied between 30 and 70%. This preliminary data shows a model with SPN3 is feasible and safe.

To increase the relevance of the EHPC model and its use for assessing future vaccines such as V114, researchers are proposing here to set up an EHPC model with carefully selected non-proprietary SPN3 strains. They will conduct a safety and dose-ranging study to determine the optimum SPN3 strain and dose for colonisation acquisition and confirm the dose in a subsequent larger cohort in a reproducibility study. They will study mucosal and systemic immune responses to this serotype and their association with protection against colonisation acquisition and clearance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/03/2022, North West-Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8118; liverpoolcentral.rec@hra.nhs.uk), ref: 22/NW/0051

Study design
Observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Pneumococcus infection

Interventions
A human challenge study to establish an SPN3 EHPC model, consisting of two parts. The first part is a dose-ranging and safety study whereby sequential cohorts of 10 healthy participants are challenged with escalating doses of SPN3. Up to two isolates of SPN3 will be tested in this part of the study. Colonisation will be determined using nasal wash sampling. Using the dose that results in ≥50% participants being colonised, with a high safety profile, the researchers will

complete the cohort with another 33 participants to check for the reproducibility of the attack rate. In the reproducibility study, various samples will be taken for the determination of both local and systemic immunological responses to pneumococcal challenge.

*An additional targeted booster inoculation will be given to participantson day 14 if theyhave tested negative for SPN3 on D2 and 7 samples. Depending on the ongoing results of the study, this second inoculation may be discontinued.

**Day 14 booster inoculation in reproducibility to be included/excluded at the discretion of the CI depending on results of the dose-ranging study. If it is included, only participants who have tested negative for SPN3 on D2 and D7 will receive the second inoculation.

***and have not subsequently had two consecutive negative nasal wash samples

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Streptococcus pneumoniae (SPN3)

Primary outcome(s)
The occurrence of experimental SPN3 colonisation of the nasopharynx, determined by SPN3 presence in classical microbiology culture in at least one nasal wash (NW) sample at any timepoint following inoculation(s) (combined and individually), e.g. day 2, day 7, day 13, day 16, day 21 or day 28. This will be assessed for each isolate and dose separately.

Key secondary outcome(s))
1. The rate of occurrence of SPN3 experimental colonisation determined by classical culture and qPCR (combined and individually) from at least one nasal wash (NW) sample at any time point following one or two inoculations (combined and individually), e.g. day 2, day 7, day 13, day 16, day 21 or day 28. This will be assessed for each isolate and dose separately.
2. The bacterial density of experimental SPN3 colonisation of the nasopharynx in NW determined by classical culture and molecular methods at each and any timepoint following one or two inoculations (combined and individually), e.g. day 2, day 7, day 13, day 16, day 21 or day 28. This will be assessed for each isolate and dose separately.
3. The duration of experimental SPN3 colonisation of nasopharynx determined by the last NW sample following one or two inoculations (combined and individually) i.e. day 13 and/or day 28 in which SPN3 is detected by classical culture or molecular methods. This will be assessed for each isolate and dose separately
4. The presence of mild or moderate symptoms as recorded on a Likert scale in participants with SPN3 within the first 7 days after inoculations. Sore throat grading score will also be used if applicable
5. Cell immunophenotyping using flow cytometry methods to identify and characterise cell populations such as neutrophils, monocytes, T cells and B cells in nasal cells samples at screening and 2, 7, 16, 21 and 28 days after the first inoculation
6. Anti-SPN3 polysaccharide specific immunoglobulin G (IgG) levels measured using ELISA on serum and nasal wash samples taken on days 2, 7 ,13, 16, 21 and 28
7. Quantification and characterization of the number of SPN3-polysaccharide specific memory B

cell populations in PBMC samples using flow cytometry methods at screening, 13 and 28 days after the first inoculation
8. 30 cytokines and chemokines measured using multiplex Luminex in nasosorption samples at screening and 2, 7, 13, 16, 21 and 28 days after the first inoculation
9. The rate of pneumococcal bacterial shedding as defined by swabs of hand and cough-plate based assessment post-inoculation (presence and density CFU/ml) at 2, 7, 13, 16, 21 and 28 days after the first inoculation (during the COVID-19 pandemic cough sampling may not be performed)
10. The rate of pneumococcal bacterial shedding as defined by exhaled detection facemask and cough-plate based assessment post- inoculation at 2 and 7 days post-inoculation (presence and density [CFU/ml])
11. The rate of occurrence and density of SPN3 colonisation post-inoculation in natural SPN carriers, identified using classical microbiology methods or qPCR at any timepoint post-inoculation
12. The presence, density and duration of SPN3 colonisation in NW and saliva samples identified using classical microbiology methods or qPCR at any timepoint post-inoculation

Completion date
22/11/2023

Eligibility

Key inclusion criteria
1. Healthy young adults aged 18-50 years (inclusive). This age range minimises the risk of invasive pneumococcal infection and allows comparison with previously published experimental work done by our group.
2. Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement, enabling valid consent to be given
3. Access to their own mobile telephone - to ensure safety and timely communication
4. Capacity to give informed consent

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
50 years

Sex
All

Total final enrolment

Key exclusion criteria

1. Currently involved in another study unless observational or non-interventional, excluding the EHPC bronchoscopy study (at the discretion of the study team). This is to ensure no harm comes to the participants through over-sampling.
2. Participant in any previous EHPC trial in the past year
3. Participant in previous EHPC trial inoculated with SPN3 in the last 3 years
4. Participant in EHPC Pneumo 2 trial
5. Vaccination: previous pneumococcal vaccination PPV23 or PCV13 (routine in babies born in the UK since 2005) or PCV10. This can be self-reported or confirmed from GP questionnaire (GPQ) if deemed necessary at clinician discretion.
6. Allergy to penicillin/amoxicillin
7. Health history (self-reported or confirmed by GPQ or medical summary if felt to be necessary at clinician discretion):
8. Chronic ill health including immunosuppressive history, diabetes, asthma (on regular medication), recurrent otitis media or other respiratory disease
9. Medication that may affect the immune system e.g., steroids, inflammation altering or disease-modifying anti-rheumatoid drugs
10. Long term use of antibiotics for chronic infection
11. Major pneumococcal illness requiring hospitalisation in the last 10 years
12. Other conditions considered by the clinical team as a concern for participant safety or integrity of the study
13. Significant mental health problems (uncontrolled condition or requiring previous admission to a psychiatric unit) that would impair ability to participate
14. Direct caring role or close contact with individuals at higher risk of infection during the inoculation period if personal protective equipment (PPE) not worn:
14.1. Children under 5 years of age
14.2. Adults with chronic ill health or immunosuppression
14.3. Hospital patients
15. Current or ex-smoker (daily cigarettes, daily e-cigarettes/vaping and daily smoking of recreational drugs) in the last 6 months. Participants who smoke <5 cigarettes per week may be included.
16. Previous significant smoking history (>20 cigarettes per day for 20 years or equivalent [>20 pack years])
17. Biologically female participants of child-bearing potential (WOCBP) who are:
17.1. Currently pregnant/lactating
17.2. Intending on becoming pregnant during the study
17.3. Not deemed to have effective birth control
18. History of or current drug or alcohol abuse:
18.1. Men should not drink >3 units/day regularly
18.2. Women should not drink >2 units/day regularly
19. Overseas travel planned in follow up period of study visits
20. Natural SPN3 colonisation in baseline nasal wash – if a participant is colonised with non-SPN3 pneumococcus, they can be included as part of exploratory analyses, but would not be included in the primary analysis
21. STOP criteria – participants who meet STOP criteria at the time of screening:
21.1. Clinical history and examination: STOP if unexplained or concerning findings on history or examination
21.2. Severe adverse event (SAE) or research-related injury (RRI): STOP if related SAE or RRI reported

21.3. Engagement with research team: STOP if the research team have concerns about the participant's ability to commit to frequent communication and safety checks
21.4. Full blood count (FBC):
21.5.1. STOP if Hb <10 g/l
21.5.2. STOP if total WCC <1.5 x 10e9/l
21.5.3. STOP if total WCC >12 x 10e9/l
21.5.4. STOP if platelets <75 x 10e9/l
21.6. Resting SpO_2: STOP if <94%
21.7. Illness during the study: STOP if participant develops a medical condition or commences medication while on a study that would meet exclusion criteria

Temporary exclusion criteria:
1. Ongoing COVID-19 symptoms (fever, cough, shortness of breath, anosmia or ageusia) or confirmed current COVID-19 infection. Participants with resolved COVID-19 after their UK Health Security Agency (UKHSA) determined isolation period has ended can be included.
2. Current/acute illness within 14 days prior to inoculation if COVID-19 negative
3. Positive COVID-19 swab whether symptomatic or asymptomatic within 10 days of inoculation
4. Currently isolating following exposure to COVID-19 as per UKHSA guidance
5. Antibiotic use within 28 days of inoculation.
6. Participants who have been temporarily excluded at screening may be re-screened at a later date to assess their eligibility at this time for inclusion into the study. At this point, the participant would be re-consented if their initial written consent was given >4 months prior to this date
7. Vaccination 21 days prior to inoculation
8. Participants that have been temporarily excluded due to a positive COVID-19 swab will require a negative lateral flow test prior to subsequent inoculation

Date of first enrolment
04/04/2022

Date of final enrolment
22/11/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Liverpool School of Tropical Medicine
Pembroke Place
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L3 5QA

Sponsor information

Organisation
Liverpool School of Tropical Medicine

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No