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Pneumonia Research: Establishing a Model Using SPN3

Submission date	Recruitment status	[X] Prospectively registered
01/05/2019	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
08/05/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
11/07/2022	Other	

Plain English summary of protocol

Background and study aims
Streptococcus pneumoniae is the leading cause of disease and death worldwide, causing community-acquired pneumonia (CAP), bacterial meningitis and sepsis. Pneumococcal infections cause over 1 million pneumonia deaths per year in children in the developing world and are a major burden of ear infections globally. The Experimental Human Pneumococcal Challenge (EHPC) Model has been developed over ten years in which healthy participants have live pneumococcal bacteria pipetted into their nose to determine colonisation rates, immune responses and test pneumococcal vaccines. In order to increase the relevance of the model and its use for vaccine development, we wish to now further develop the EHPC model to include other strains of pneumococcus that are commonly found in the community. In this study, we will establish safe colonisation with SPN3.

Who can participate?
Healthy adults aged 18 - 69 years can take part.

What does the study involve?
The initial stage of the study involves healthy volunteers 18-50yrs old. These participants will be nasally inoculated with a dose of live pneumococcal bacteria: SPN3. The dose inoculated will be either 20,000 or 80,000 or 160,000 CFU/0.1ml per nostril. Groups of 10 participants will be inoculated with each dose to achieve a colonisation rate of ≥40%. A lower dose of 10,000 CFU/0. 1ml per nostril may also be used in 10 participants if the colonisation rates of the earlier doses are low. Participants are followed up during clinic visits to confirm that they are well at Day 2, Day 7 and Day 14. Research samples are taken during these visits and may include throat swabs, urine, blood, saliva, nasal wash (squirting some salty water into the nose and collecting the liquid) and nasal cell samples (a small scratch inside the nose).
Once the optimum dose has been selected by the Trial Steering Group, a further 33 healthy participants will be nasally inoculated using this dose. This stage of the study can be repeated with a second isolate of SPN3 if the colonisation rates are low.
Following the first stage to determine the optimum isolate and dose, 10 healthy older adults aged 60-69years old will be nasally inoculated with the selected isolate and dose to confirm colonisation and safety.
All participants will attend a screening appointment prior to inoculation and will be followed up

in clinic at Day 2, Day 7 and Day 14 at which point they will be given a 3-day course of amoxicillin to take if they have tested positive for pneumococcal colonisation (SPN3) at any point following the nasal inoculation.

What are the possible benefits and risks of participating?
There are no direct benefits to taking part in the study however we hope that participants will feel that they have contributed to a research project that could inform future vaccine research and development.
The risks associated with the research relate to the sampling methods and the inoculation of live bacteria. These are as follows:
Nasal wash samples involve squirting some sterile saline inside the nose, this is then expelled and collected for processing. Some participants may swallow some of the saline however this is not uncomfortable.
Blood sampling, we take a small sample of blood at the beginning of the study (up to 50ml). Some participants may find this temporarily uncomfortable however the staff that perform this are trained and experienced in this process. On occasions, blood sampling can cause a small bruise or make the participant feel light headed. The volume taken during this study is highly unlikely however to make participants feel light headed.
Throat swab may make the participant gag a little.
There are no adverse effects of the saliva and urine samples.
Nasal cell sampling can cause discomfort however this is temporary, it is likely to make the participant's eyes water and can occasionally cause slight bleeding evident on the sample probe. It is not likely to cause an actual nose bleed.
The risks associated with the inoculation of live bacteria include pneumonia, meningitis or sepsis. We have however inoculated over 1400 healthy participants in 9 years and we have not experienced a single case of these diseases. We reduce the risk by providing the participant with 24/7 access to a member of the research team, a course of antibiotics to be taken in case of illness (under specific guidance of the research team), a safety information leaflet and a digital thermometer to check their temperature daily for the first 3-4 days and in the case of feeling unwell.

Where is the study run from?
Accelerator Research Clinic, Liverpool School of Tropical Medicine, UK.

When is the study starting and how long is it expected to run for?
The study is planned to start in June 2019 and is expected to run for up to 2 years or until the recruitment target has been reached. Each participant is expected to remain in the study for 3-4 weeks

Who is funding the study?
Pfizer UK

Who is the main contact?
Dr Ryan Robinson
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Study website
https://www.lstmed.ac.uk/pneumoniavaccine

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Version 1: 18/03/2019

Study information

Scientific Title
Experimental Human Pneumococcal Challenge (EHPC) Model: Establishing SPN3 Challenge Model

Acronym
EHPC: SPN3

Study objectives
To determine the optimum dose and isolate of SPN3 to establish colonisation in healthy adults by classical culture of the nasopharynx using the Experimental Human Pneumococcal Challenge (EHPC) model.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 26/06/2019, North West - Liverpool East Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ; 0207104 8345; 0207 104 8019; nrescommittee.northwest-liverpooleast@nhs.net), ref: 19/NW/0238, IRAS 263376

Study design
Interventional non-randomised study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
The initial stage of the study involves healthy volunteers 18-50yrs old. These participants will be nasally inoculated with a dose of live pneumococcal bacteria: SPN3. The dose inoculated will be either 20,000 or 80,000 or 160,000 CFU/0.1ml per nostril. Cohorts of 10 participants will be inoculated with each dose to achieve a colonisation rate of ≥40%. A lower dose of 10,000 CFU/0.1ml per nostril may also be used in 10 participants if the colonisation rates of the earlier doses are low.
Once the optimum dose has been selected by the Trial Steering Group, a further 33 healthy participants will be nasally inoculated using this dose. This stage of the study can be repeated with a second isolate of SPN3 if the colonisation rates are low.
Following the first stage to determine the optimum isolate and dose, 10 healthy older adults aged 60-69years old will be nasally inoculated with the selected isolate and dose to confirm colonisation and safety.
All participants will attend a screening appointment prior to inoculation and will be followed up in clinic at Day 2, Day 7 and Day 14 at which point they will be given a 3-day course of amoxicillin to take if they have tested positive for pneumococcal colonisation (SPN3) at any point following the nasal inoculation.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Pneumococcal bacteria serotype 3

Primary outcome measure
The presence of SPN3 pneumococcal bacteria in nasal wash recovered by classical microbiological culture at any timepoint post inoculation: Day 2, Day 7 or Day 14. This will be reported as yes or no.

Secondary outcome measures
1. Density of bacteria recovered from nasal wash by classical microbiological culture in positive participants, this will be reported as colony forming units (CFU) per ml of nasal wash.
2. The presence of SPN3 pneumococcal bacteria in nasal wash recovered by molecular methods at any timepoint post inoculation: Day 2, Day 7 or Day 14. This will be reported as yes or no.

Overall study start date
03/08/2018

Completion date
23/06/2021

Eligibility

Key inclusion criteria
1. Healthy young adults aged 18-50 years (inclusive) - ages chosen to minimise the risk of pneumococcal infection, and to allow comparison with previously published experimental work done by our group.
2. Healthy older participants group only- adults aged 60-69 years (inclusive)
3. Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement
4. Access to their own mobile telephone - to ensure safety and timely communication
5. Capacity to give informed consent

Participant type(s)
Healthy volunteer

Age group
Mixed

Lower age limit
18 Years

Upper age limit
69 Years

Sex
Both

Target number of participants
156

Total final enrolment
96

Key exclusion criteria
1. Currently involved in another study unless observational or non-interventional except for the EHPC bronchoscopy study*
2. Participant in a previous EHPC trial within the last 3 years (at the discretion of the study team ie. Not inoculated nasally with pneumococcus)
3. Vaccination: previous pneumococcal vaccination PPV23 or PCV13 (routine in UK babies born since 2005 or US 2001) or PCV10.
4. Allergy: to penicillin or amoxicillin
5. Chronic ill health including, immunosuppressive history, diabetes, asthma (on regular medication), recurrent otitis media or other respiratory disease
6. Medication that may affect the immune system e.g. steroids, inflammation altering (e.g. nasal steroids, roacutane) or disease-modifying anti-rheumatoid drugs.
7. Recent antibiotics (within the last 28 days or long term for known active chronic infection)
8. Current illness or acute illness within 14 days prior to inoculation
9. Major pneumococcal illness requiring hospitalisation
10. Other conditions considered by the clinical team as a concern for participant safety or integrity of the study
11. Direct caring role or close contact with individuals at higher risk of infection (children under 5 years age, chronic ill health or immunosuppressed adults)
12. Current or ex-smoker (regular cigarettes, regular e-cigarette/vaping and regular smoking of recreational drugs) in the last 6 months
13. Previous significant smoking history - more than 20 cigarettes per day for 20 years or the equivalent (>20 pack years)
14. Women of child-bearing potential (WOCBP) who are:
14.1 Not deemed to have sufficient/effective birth control or confirmed abstinence
14.2 Pregnant
15. History or current drug or alcohol abuse (frequently drinking alcohol: men and women should not regularly drink >3 units/day and >2 units/day respectively) at discretion of the clinician
16. Overseas travel planned in follow up period of the study visits
17. Natural pneumococcal colonisation at baseline It is anticipated that 10-15% of screened participants will have natural pneumococcal colonisation at the time of recruitment as demonstrated by the initial nasal wash. These individuals will be excluded from the study after screening visits.

Date of first enrolment
24/06/2019

Date of final enrolment
23/06/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Accelerator Research Clinic
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L7 8XZ

Sponsor information

Organisation
Liverpool School of Tropical Medicine

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Sponsor type
University/education

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Industry

Funder Name
Pfizer UK

Alternative Name(s)
Pfizer Ltd, Pfizer Limited

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
We plan to publish the results in scientific peer-reviewed journals, national and international conferences, on our website and summaries to be included in our yearly newsletter that is used at public engagement events and sent to all participants electronically.

Intention to publish date
23/06/2022

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
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1	18/03/2019	23/05/2019	No	Yes
Participant information sheet	version V1	18/03/2019	23/05/2019	No	Yes
Results article		08/07/2022	11/07/2022	Yes	No
HRA research summary			28/06/2023	No	No