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A pneumococcal human challenge study in adults aged 50-84 years

Submission date
26/03/2024

Recruitment status
No longer recruiting

Registration date
12/04/2024

Overall study status
Ongoing

Last Edited
28/01/2026

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
The germ ‘pneumococcus’ (Streptococcus pneumoniae, a bacteria) is a major cause of pneumonia, meningitis and sepsis around the world leading to over a million deaths per year. The biggest impact is on young children and older adults, especially in low-income countries. However, most of the information that we have about how the body responds to this infection comes from younger adults. These younger adults are less likely to develop severe infection and how they respond to bugs is different to how older adults respond. This study looks at how pneumococcus lives in the noses of older adults and causes infection. The aim is to better understand how this bug affects older people, which will hopefully help us design medication and vaccinations better for this age group.

Over the past decade, the research group has developed innovative methods to study pneumococcus infection in healthy volunteers. People are carefully screened for safety and then infected (“challenged”) with small amounts of bacteria in their nose, which allows us to understand why some people who are exposed to the bacteria develop infection whilst others don’t. This kind of study (a “human challenge” study) can improve understanding of how bugs cause disease and is a cost-efficient way of designing and testing drugs and vaccinations. To date, over 2000 participants have been challenged with pneumococcus, including older people, demonstrating that these studies can be done safely without harm to participants. In this study, older adults will be given pneumococcus in their noses so that tests can be run to see how the bug affects them and sticks to their noses. Samples will be taken throughout the study to understand how the immune system responds to it.

Who can participate?
Healthy older adults and seniors aged 50-84 (inclusive) years old

What does the study involve?
All participants are screened to check they are eligible for the study and are not at high risk of infection. Following this, they will have a clinical examination and nasal and blood tests. All participants are exposed (‘challenged’) to the pneumococcus germ through drops in the nose.

The study involves a further 6 in-person visits (7 visits including the initial visit above). These are spaced out over approximately 4 weeks. At these visits, participants are checked for any symptoms and will have certain nasal and blood samples taken.

What are the possible benefits and risks of participating?
Participants will be a valuable part of a research study that is hoped will eventually lead to the development of new methods to prevent or treat respiratory infections.

Safety will be paramount in this study. Participants will have access to a study doctor 24/7 and be given backup antibiotics to take if needed. The team will work closely with participants so that they understand the study requirements and will address their questions and concerns.

Challenge pneumococcal bacteria: Because the germ participants are exposed to is live, there is a very small risk of infection to them or their close contacts. However, the germ has been used in previous studies in older adults with no serious side effects. They may however get cold-like symptoms, headaches, earaches, a cough or a fever.

A safety pack is provided and they will have 24-hour access to the research team by phone. This includes clear safety precautions and what to do if they feel unwell. Everyone who tests positive for the pneumococcus germ will take a course of antibiotics at the end of the study, or if they feel unwell, before that.

Blood sampling: The risks associated with blood sampling are minimal, but this may cause temporary pain, bruising and/or bleeding to the arm. The blood sampling will be performed by trained healthcare professionals. In the rare circumstance that anything unusual or medically significant is noticed about your blood then the team will inform them and ask their permission to inform your GP.

Nasal sampling: There are limited risks related to these samples. During a nasal wash, you may swallow a small amount of salty water, however, this is harmless. The nasal cell sample is slightly uncomfortable and may make your eyes water briefly. Sometimes a small amount of blood can be seen on the sample probe, however, it is rare for it to cause a nosebleed.

Incidental medical findings
Since several medical tests are carried out throughout the study, previously unknown health issues (e.g. high blood pressure or abnormal blood results) may be detected. This will be discussed with the participant and with their permission, their GP informed for ongoing follow-up.

Where is the study run from?
The study is run by the Liverpool Vaccine Group at the Liverpool School of Tropical Medicine in Liverpool, UK. We have been studying lung infections using healthy volunteers for over ten years to provide world-leading research into the pneumococcus germ using methods called an Experimental Human Pneumococcal Challenge (EHPC) model. More than 2000 participants have already been safely studied using our methods, including older adults.

When is the study starting and how long is it expected to run for?
October 2023 to January 2026

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

Who is the main contact?
Dr Oliver Hamilton, Oliver.hamilton@lstmed.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
340045

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
24-004, IRAS 340045, CPMS 61054

Study information

Scientific Title
Experimental human pneumococcal challenge in older adults

Acronym
Ages-2

Study objectives
The primary aim of this exploratory study is the detection of pneumococcus within nasal cells using confocal microscopy and comparing this against data from younger adults

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 29/02/2024, East of England - Cambridge South Research Ethics Committee (Equinox House City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8084; cambridgesouth.rec@hra.nhs.uk), ref: 24/EE/0038

Study design
Single-centre open-label controlled human-challenge study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Pneumoccocal carriage

Interventions
Current interventions as of 10/03/2025:
This is a single-centre, open-label controlled human infection study in older healthy participants using a previously established and safe model of pneumococcal challenge across two phases. Participants will be older adults and seniors aged 50-84 years old. All participants will be inoculated with live pneumococcus and followed up for evidence of pneumococcal carriage and immune responses through mucosal and systemic sampling.

In Phase A, healthy participants will undergo a challenge with Streptococcus pneumoniae serotype 6B (Spn6B) BHN418 strain at a dose of 80,000 colony-forming units (CFU)/naris. This will be administered intra-nasally using a P200 micropipette to give 0.1ml of pneumococcus-containing fluid instilled into each nostril in our human challenge facility. This will occur once during the study in all participants, who will not be randomised or blinded to the intervention. All participants will be followed up for 28 days at Day 2, 6, 9, 14 and 28.

Phase B will be identical to Phase A, except the inoculum will be Streptococcus pneumoniae serotype 3 (Spn3) LIV014-S3 strain at the same dose of 80,000CFU/naris

Previous interventions:
This is a single-centre, open-label controlled human infection study in older healthy participants using a previously established and safe model of pneumococcal challenge. Participants will be older adults and seniors aged 50-84 years old. All participants will be inoculated with live pneumococcus (serotype 6B) and followed up for evidence of pneumococcal carriage and immune responses through mucosal and systemic sampling.

Healthy participants will undergo a challenge with Streptococcus pneumoniae serotype 6B (Spn6B) BHN418 strain at a dose of 80,000 colony-forming units (CFU)/naris. This will be administered intra-nasally using a P200 micropipette to give 0.1ml of pneumococcus-containing fluid instilled into each nostril in our human challenge facility. This will occur once during the study in all participants, who will not be randomised or blinded to the intervention. All participants will be followed up for 28 days at Day 2, 6, 9, 14 and 28.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Streptococcus pneumoniae serotype 6B (Spn6B) BHN418 strain, Streptococcus pneumoniae serotype 3 (Spn3) LIV014-S3 strain

Primary outcome(s)
The detection of pneumococcus within nasal epithelial cells, obtained through minimally-invasive superficial nasal scrape biopsies, measured using confocal microscopy and association with nasal colonisation outcome (measured by classical microbiology and multiplex PCR) following pneumococcal inoculation within 28 days from pneumococcal challenge.

Key secondary outcome(s))
Current secondary outcome measures as of 10/03/2025:
The following secondary outcome measures are assessed at Day 2, 6, 9, 14 and 28 post pneumococcal challenge:
1. Rates of colonization by pneumococcus and its density and duration by detection of pneumococcus serotype 6B (Phase A) or serotype 3 (Phase B) from one or more nasal wash samples by microbiological culture or multiplex qPCR in the 28 days following the initial pneumococcal challenge
2. Changes in the population of immune/inflammatory cells, specifically innate immune cell dynamics, activation and functionality in the nasal mucosa, in response to challenge and/or colonisation, measured using immunophenotyping on nasal epithelial cell samples
3. Quantification of a systemic and mucosal humoral immune response to nasopharyngeal (NP) carriage by measuring pneumococcal serotype-specific antibodies on nasal and blood samples using ELISAs
4. Quantification of a systemic and mucosal cellular immune response to NP carriage by measuring pneumococcal-specific T-cell recall responses using immunophenotyping
5. Demonstration of functional activity of participant anti-pneumococcal antibodies measured using assays including opsonophagocytic killing assays

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The following secondary outcome measures are assessed at Day 2, 6, 9, 14 and 28 post pneumococcal challenge:
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4. Quantification of a systemic and mucosal cellular immune response to NP carriage by measuring pneumococcal-specific T-cell recall responses using immunophenotyping
5. Demonstration of functional activity of participant anti-pneumococcal antibodies measured using assays including opsonophagocytic killing assays

Completion date
11/12/2026

Eligibility

Key inclusion criteria
1. Healthy adults aged 50-84 (inclusive, at the time of consent and inoculation) years old
2. World Health Organisation performance status 0 (able to carry out all normal activity without restriction) or 1 (restricted in strenuous activity but ambulatory and able to carry out light work)
3. Access to telephone and e-mail
4. Fluent spoken English – to ensure a comprehensive understanding of the research project
5. Capacity to provide written informed consent in English

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 years

Upper age limit
84 years

Sex
All

Total final enrolment
30

Key exclusion criteria

Current exclusion criteria as of 20/08/2025:
Individuals may not participate in the study if they are/have:

Research participant:
1. Currently involved in another study unless observational or non-interventional, excluding the EHPC bronchoscopy study (at the discretion of the study team) and exceptions may be applied at the discretion of the CI/PI to ensure no harm comes to the participants (e.g. excessive blood or nasal sampling)
2. Participated in a previous Spn6B/Spn3 EHPC study within 3 years

Nasal carriage:
Participants who have natural pneumococcal identified at screening

Vaccination:
1. Had any vaccination within 28 days of enrolment (defined as the time of inoculation) other than against influenza or COVID-19, which is permissible up to 14 days before inoculation
2. Had a pneumococcal conjugate vaccine*

Allergy:
Allergy to beta-lactam antibiotics (including penicillin and amoxicillin)

Medical history leading to increased risk of severe infection, illness, including but not limited to:
1. Asplenia or dysfunction of the spleen
2. Chronic respiratory disease (e.g. asthma [requiring medication (including salbutamol inhaler) within the last 12 months], COPD, bronchiectasis)
3. Chronic heart disease (e.g. angina, ischaemic heart disease, chronic heart failure) - controlled and stable hypertension may be included
4. Chronic kidney disease (e.g. kidney transplant, regular dialysis, CKD3-5)
5. Chronic liver disease (e.g. cirrhosis, hepatitis)
6. Chronic neurological disease that limits mobility, bulbar or respiratory function (including stroke, Parkinson's disease, dementia and multiple sclerosis)
7. Diabetes mellitus (including diet controlled)
8. Cancer within the past 5 years (except for basal cell carcinoma of the skin, melanoma in situ and cervical carcinoma in situ)
9. Receipt of immunosuppressive therapy such as anti-cancer immunotherapy, chemotherapy or radiation therapy within the preceding 5 years or long-term systemic corticosteroid, Roaccutane, or disease-modifying anti-rheumatoid drugs therapy (for more than 7 consecutive days within the 3 months before enrolment)
10. Individuals with cochlear ear implants
11. Individuals with major cerebrospinal fluid leaks (e.g. following traumatic, major skull surgery, or requiring CSF shunts)
12. Subjects with known or suspected immune deficiency (e.g. HIV, known IgA deficiency, immotile cilia syndrome, or Kartagener's syndrome)
13. History of frequent nose bleeds within the last 2 years
14. Bleeding disorders
15. Significant mental health disorders
16. Other uncontrolled comorbidities, as determined by the clinical investigator, which would be expected to increase the risk of pneumococcal disease
17. Any major pneumococcal illness or pneumonia requiring hospitalisation in the last 10 years
18. Meeting STOP criteria

Medication:
1. Any medication that may affect the immune system in the last 3 months (e.g. systemic steroids [IM/IV], steroid nasal spray, Roaccutane, disease-modifying anti-rheumatoid drugs)
2. Long-term antibiotic use or any antibiotics (other than topical) in the past 28 days
3. Recipient of monoclonal antibodies in the last 6 months for any indication
4. Recipient of blood transfusion products within the last year
5. Any medication that may affect the coagulation system in the last 3 months (excluding low-dose aspirin)
6. Use of any medication or other product (prescription or over-the-counter) for symptoms of rhinitis or nasal congestion within the last 1 month, except for anti-histamines for hayfever, which are permissible.

Maternity:
1. Pregnancy
2. Lactation
3. Intend to become pregnant during the study
4. Female participants of child-bearing potential** unable to take effective contraception measures***

Direct caring role or share living accommodation with individuals at a higher risk of infection:
1. Children ≤5 years of age
2. Adults with immunosuppression
3. Adults at high risk of invasive pneumococcal disease at the discretion of the investigator
4. Adults classified as clinically extremely vulnerable by the National Health Service
5. Health-care worker (unless willing to wear a surgical face mask at all times with patients, in Phase A only, health-care workers are excluded from Phase B)

Smoking:
1. Current or ex-smoker (regular cigarettes [≥5 per week] /cigars/e-cigarette/vaping/smoking of recreational drugs) in the last 6 months
2. Previous significant smoking history (>20 pack-year history of smoking OR 5-20 pack-year history of smoking but quit less than five years ago [One pack-year is defined as smoking 20 cigarettes per day for one year])

Current alcohol and recreational drug use:
1. Regularly drinks >21 units alcohol (men) or >14 units alcohol (women) per week
2. Regularly uses recreational drugs

Overseas travel planned within the study period (28 days after the primary challenge)

Any other issue which, in the opinion of the study staff, may:
1. Put the participant or their contacts at risk because of participation in the study
2. Adversely affect the interpretation of the study results, or
3. Impair the participant's ability to participate in the study

*However, previous pneumococcal polysaccharide vaccination (PPV) will not be an exclusion criterion as this vaccine does not confer protection against mucosal carriage and will therefore not impact on our primary outcome measure. We will endeavour to document the vaccination status of all participants to explore the potential for confounding within the study.

**A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient.

*** Acceptable effective forms of contraception for female volunteers include:
1. Established use of oral, injected or implanted hormonal methods of contraception
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
3. Total abdominal hysterectomy
4. Bilateral tubal occlusion
5. Barrier methods of contraception (condom or occlusive cap with spermicide)
6. Male sterilisation, if the vasectomised partner is the sole partner for the subject
7. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments (for this trial from inoculation until D28). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Previous exclusion criteria as of 10/03/2025:
Individuals may not participate in the study if they are/have:

Research participant:
1. Currently involved in another study unless observational or non-interventional, excluding the EHPC bronchoscopy study (at the discretion of the study team) and exceptions may be applied at the discretion of the CI/PI to ensure no harm comes to the participants (e.g. excessive blood or nasal sampling)
2. Participated in a previous Spn6B/Spn3 EHPC study within 3 years

Nasal carriage:
Participants who have natural pneumococcal identified at screening

Vaccination:
1. Had any vaccination within 28 days of enrolment (defined as the time of inoculation) other than against influenza or COVID-19 which is permissible up to 14 days before inoculation
2. Had a pneumococcal conjugate vaccine*

Allergy:
Allergy to beta-lactam antibiotics (including penicillin and amoxicillin)

Medical history leading to increased risk of severe infection, illness including but not limited to:
1. Asplenia or dysfunction of the spleen
2. Chronic respiratory disease (e.g. asthma [requiring medication (including salbutamol inhaler) within last 12 months], COPD, bronchiectasis)
3. Chronic heart disease (e.g. angina, ischaemic heart disease, chronic heart failure) - controlled and stable hypertension may be included
4. Chronic kidney disease (e.g. kidney transplant, regular dialysis, CKD3-5)
5. Chronic liver disease (e.g. cirrhosis, hepatitis)
6. Chronic neurological disease that limits mobility, bulbar or respiratory function (including stroke, Parkinson’s disease, dementia and multiple sclerosis)

7. Diabetes mellitus (including diet controlled)
8. Cancer within the past 5 years (except for basal cell carcinoma of the skin, melanoma in situ and cervical carcinoma in situ)
9. Receipt of immunosuppressive therapy such as anti-cancer immunotherapy, chemotherapy or radiation therapy within the preceding 5 years or long-term systemic corticosteroid, Roaccutane, or disease-modifying anti-rheumatoid drugs therapy (for more than 7 consecutive days within the 3 months before enrolment)
10. Individuals with cochlear ear implants
11. Individuals with major cerebrospinal fluid leaks (e.g. following traumatic, major skull surgery, or requiring CSF shunts)
12. Subjects with known or suspected immune deficiency (e.g. HIV, known IgA deficiency, immotile cilia syndrome, or Kartagener's syndrome)
13. History of frequent nose bleeds within the last two years
14. Bleeding disorders
15. Significant mental health disorders
16. Other uncontrolled comorbidities, as determined by the clinical investigator, which would be expected to increase the risk of pneumococcal disease
17. Any major pneumococcal illness or pneumonia requiring hospitalisation in the last 10 years
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Medication
1. Any medication that may affect the immune system in the last 3 months (e.g. systemic steroids [IM/IV], steroid nasal spray, Roaccutane, disease-modifying anti-rheumatoid drugs)
2. Long-term antibiotic use or any antibiotics (other than topical) in the past 28 days
3. Recipient of monoclonal antibodies in the last six months for any indication
4. Recipient of blood transfusion products within the last year
5. Any medication that may affect the coagulation system in the last 3 months (excluding low-dose aspirin)
6. Use of any medication or other product (prescription or over-the-counter) for symptoms of rhinitis or nasal congestion within the last 1 month

Maternity:
1. Pregnancy
2. Lactation
3. Intend to become pregnant during the study
4. Female participants of child-bearing potential** unable to take effective contraception measures***

Direct caring role or share living accommodation with individuals at a higher risk of infection
1. Children ≤5 years of age
2. Adults with immunosuppression
3. Adults at high risk of invasive pneumococcal disease at the discretion of the investigator
4. Adults classified as clinically extremely vulnerable by the National Health Service
5. Health-care worker (unless willing to wear a surgical face mask at all times with patients)

Smoking
1. Current or ex-smoker (regular cigarettes [≥5 per week] /cigars/e-cigarette/vaping/smoking of recreational drugs) in the last 6 months
2. Previous significant smoking history (more than 5 cigarettes per day for 20 years or the equivalent [i.e. >5 pack years])

Current alcohol and recreational drug use
1. Regularly drinks ≥ 14 units/week (male or female)
2. Regularly uses recreational drugs

Overseas travel planned within the study period (28 days after the primary challenge)

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Date of first enrolment
01/04/2024

Date of final enrolment
18/11/2025

Locations

Countries of recruitment
United Kingdom

England

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

Sponsor information

Organisation
Liverpool School of Tropical Medicine

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon reasonable request for anonymised data from participants who have consented to sharing their samples for future research from Prof. Daniela Ferreira (daniela.ferreira@paediatrics.ox.ac.uk). The data will be available for request after primary, secondary and exploratory aims have been addressed. A data sharing agreement must be signed before data are made available.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	06/03/2024	02/04/2024	No	Yes
Participant information sheet	version 2.1	04/08/2025	20/08/2025	No	Yes
Protocol file	version 4.0	08/07/2025	20/08/2025	No	No