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Experimental human pneumococcal challenge in chronic obstructive pulmonary disease and cigarette smoking

Submission date
13/08/2018

Recruitment status
Suspended

Registration date
27/09/2018

Overall study status
Suspended

Last Edited
14/04/2022

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
The researchers are studying bacteria called pneumococcus. They think that small numbers of bacteria present in the nose (nasal colonisation) may protect people against disease. Small numbers of these bacteria are often found in the nose of healthy adults (at least once per year) and more often in children. Usually, the carrier does not know the bacteria are there but, in some people, it can cause illness. Mild infections with pneumococcus are very common, such as ear infections in children. Pneumococcus can also infect the lung (causing pneumonia). More severe infections of the brain (causing meningitis) or the blood (causing sepsis) are very uncommon in healthy adults: about 50 cases in Liverpool per year. Very young children and adults who are elderly or those who have other illnesses are more likely to become ill. Smokers and patients with chronic obstructive pulmonary disease (COPD) are also more susceptible.

Who can participate?
Smokers aged 18-50 and patients with COPD aged 50-84

What does the study involve?
A small number of bacteria are put in the noses of the participants, similar to the amount commonly carried by healthy adults. Urine, blood, saliva, nasal and throat samples are taken to help researchers to understand more about the immune responses and inflammatory process and help to develop better vaccines for the future.

What are the possible benefits and risks of participating?
This study allows the researchers to learn about the protective mechanism that occurs in the nasal lining and use this later in the development of a new vaccine against pneumonia. More than 1000 participants have already been studied safely using this method of putting bacteria in the nose.

Where is the study run from?
The study will be conducted at the Liverpool School of Tropical Medicine with clinical procedures being undertaken in the Liverpool Life Sciences Accelerator Building's Accelerator Research Clinic (ARC) which is a LSTM sponsored research clinic on a NHS site.

When is the study starting and how long is it expected to run for?
August 2018 to September 2023

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

Who is the main contact?
1. Dr Angela Hyder-Wright
angela.hyder-wright@lstmed.ac.uk
2. Dr Andrea Collins
andrea.collins@lstmed.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Angela Hyder-Wright

Contact details
Respiratory Infection Group
Department of Clinical Sciences
LLSA
Liverpool School of Tropical Medicine
1 Daulby St
Liverpool
United Kingdom
L7 8XZ
+44 (0)7919 480 736
angela.hyder-wright@lstmed.ac.uk

Type(s)
Scientific

Contact name
Dr Andrea Collins

Contact details
Respiratory Infection Group
Department of Clinical Sciences
LLSA
Liverpool School of Tropical Medicine
1 Daulby St
Liverpool
United Kingdom

L7 8XZ
+44 (0)151 7029439
andrea.collins@lstmed.ac.uk

Additional identifiers

Protocol serial number
38984

Study information

Scientific Title
Experimental Human Pneumococcal Challenge (EHPC) in Chronic Obstructive Pulmonary Disease (COPD) and cigarette smoking

Study objectives
Individuals that smoke may have an alteration in mechanical, cellular and soluble factors which can lead to an increase in transfer of organisms to the lungs when compared with healthy individuals. The trialists hypothesize that this is likely to impact on colonisation rates and likelihood of progression to lower airway disease.

The effect of smoke on lung immunity reduces the macrophage killing activity of bacteria which increases the risk of respiratory infection. Individuals with COPD have a different oral, nasopharyngeal and lower airway microbiome when compared with healthy individuals. Lower airway colonisation may occur and promote exacerbation of chronic lung disease. It is unknown if upper airway mucosal colonisation has a protective effect similar to that in healthy individuals. The trialists hypothesize that these factors will impact colonisation rates and likelihood of progression to lower airway disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool east REC, 11/09/2018, ref: 18/NW/0479

Study design
Observational; Design type: Case-controlled study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Streptococcus pneumoniae infection in smokers and people with chronic obstructive pulmonary disease (COPD)

Interventions

Duration 24 months
Type Cohort study of human participants divided into 2 groups:
Group 1: Participants that smoke - regularly smoke a mean average of ≥5 cigarettes per day for the preceding 3 months but < 20 pack year cigarette smoking history [aged 18-50 years]
Group 2: Participants with COPD (pack year cigarette smoking history≥ 20 pack years with obstructive spirometry and either ex- or current smoker) [aged 50-84 years]
All participants will be inoculated with Streptococcus pneumoniae in the nasopharynx, with assessment of laboratory measures of the acquisition of nasal pneumococcal colonisation, and of immune response.

Participants and Timelines

The trialists will inoculate healthy smoking adult participants aged 18-50 years, patients with COPD (ex- and current cigarette smokers 50-84 years) with pure culture of a well-characterised, fully sequenced penicillin-sensitive pneumococcal serotype (6B) and observe them for the development of pneumococcal colonisation.

Study visits may take place within 7 days of the proposed date to accommodate for issues /events participants may experience that may prevent them from attending (e.g. illness, bereavement and travel issues)
Single Centre Study: Accelerator Research Clinic (ARC), LLSA at LSTM.

Assessment will be completed in stages:
1. Pre-screening: study nurse or doctor checks that the potential participant meets all the general screening criteria
2. Baseline tests: participant undergoes all general baseline tests. If any STOP criteria are met, the participant exits the study
3. Risk assessment: participant risk is stratified. Depending on the stage of the study, higher risk individuals may be postponed until after lower risk participants have been inoculated, and safety demonstrated

Confirmation of COPD diagnosis
All participants with a presumed/previous diagnosis of COPD study will undergo confirmation of that diagnosis using spirometry as an objective measurement. Spirometry is a basic breathing test which measures the amount of air that can be blown out of the lungs. This is done using a spirometer and participant's will be asked to take a deep breath in and blow into the spirometer as hard and fast as they can, until their lungs are completely empty. This test will be repeated to ensure the results are consistent. Depending on the results participant's may be given an inhaler (bronchodilator) and have the test repeated 15-20 minutes later to see if there is any change in airway obstruction. This is called reversibility. This test forms part of standard COPD diagnosis and management. In line with current guidance, post-bronchodilator FEV1/FVC < 0.7 will be used as confirmation of the presence of COPD.
If there is evidence of severe obstruction (FEV1 <50% predicted post bronchodilator) participants will be excluded from the study. Reversibility of >15% of the baseline FEV1 suggests a diagnosis of asthma and would lead to exclusion from the study.

GP Questionnaires
Although this study is not a CTIMP, and therefore GP questionnaires (GPQs) are not an obligatory requirement for participants undergoing this study, it is likely that the trialists will need to liaise with COPD participants' GPs regarding their vaccination history and current medications. Therefore, the trialists propose to send COPD participants' GPs a letter requesting that they confirm (by printing out the relevant sections of that patients' electronic medical

record, if necessary) whether the participant has received any pneumococcal vaccination and what medications they are currently prescribed. This can be extended to participants that smoke if deemed necessary by the PI.

At time of consent:
1. Participants will be asked questions to ensure they meet the inclusion and do not meet any of the exclusion criteria; this may involve discussion about ongoing medical/health issues.
2. The assessment of eligibility process will be conducted by one of the research doctors/ nurses who are formally delegated by the Principal Investigator, trained in GCP and understand the trial protocol, any queries about possibly eligibility will be discussed with the Principle Investigator.

Pre-screening and sampling methods:
Pre-screening is conducted to confirm and ensure the participant is generally healthy in the case of the smokers and in the case of the participants with COPD, to confirm a diagnosis and check severity of COPD as per current guidelines and ensure the participant is generally healthy.
1. Clinical examination: The initial clinic visit will include a focused clinical history and targeted clinical examination involving recording and evaluating vital signs including heart rate, blood pressure, temperature and oxygen saturations. Additionally, participants will have auscultation of the lung fields and heart sounds. MRC breathlessness score will be completed.
2. Spirometry: A breathing test will be performed in all participants with MRC breathlessness score >1 and all COPD participants. Spirometry with reversibility is used to confirm a diagnosis of COPD in participants and to exclude asthma.
3. Electrocardiography: This will be performed to assess for any underlying cardiac conduction and ischaemic abnormalities in participants with previous or confirmed diagnosis of COPD (obstructive spirometry)

Should a previously unrecognised abnormality be identified this will be explained to the individual, and all relevant results will be forwarded to their GP so that appropriate investigations and follow-up can be arranged. Further participation will be determined at the discretion of the study doctor.

Clinical Sampling
Urine – up to 20 ml of midstream urine is collected in all participants at pre-screening visit to test for nicotine (urine cotinine test) and pregnancy testing in females. In the event that a participant is unable to provide a sample this test will be completed on the next visit prior to inoculation. In the event that screen visit occurs >2 weeks after the pre-screen visit, the urine pregnancy test may be repeated.
Oropharyngeal swabs – The participant's tongue will be depressed using a tongue depressor exposing the palatopharyngeal arch. Samples will be obtained for detection of viral and bacterial pathogens by microbiological and molecular techniques. The sample is taken by making 5 small circular motions of the palatopharyngeal arch in contact with the mucosa whilst avoiding the patients tongue. Performing throat swabs prior to nasal washes will ensure that the oropharynx is not inadvertently contaminated with nasal pathogens prior to throat swab sampling. Up to 2 swabs may be taken at each time point as indicated.
Nasosorption – Concentrated nasal lining fluid will be obtained for cytokine analysis using nasosorption strips (similar to blotting paper) developed by Hunt Developments Ltd (UK). Strips will be held inside the nose for 1-3 minutes, then stored at -80oC pending cytokine analysis.
Nasal wash – will be performed using a modified Naclerio method. This is a well-used and validated technique to collect nasal bacterial specimens with which we now have 4 years' experience. Briefly, 5ml of saline is instilled and held for a few seconds in the nares before being expelled in to a sterile Galli pot; this is usually repeated up to 20ml in total. In the event of nasal wash loss (defined as cough/sneeze/swallow) the procedure may then be repeated to obtain an

adequate specimen.
Nasal cells – After nasal wash, nasal cells will be collected using a nanosampling method in which cells are obtained through minimally-invasive superficial nasal scrape biopsies (rhinoprobe) and participants can be biopsied multiple times with no significant side effects. Up to 4 samples will be obtained at each nasal sampling visit. If no cells are visible on the rhinoprobe following sampling, the sample can be repeated immediately.
Blood sampling – Venepuncture will be performed by trained, experienced staff. Up to 50mL of blood will be collected to measure full blood count (for safety), and laboratory measures including, but not limited to: serum immunoglobulins, genotyping, peripheral blood mononuclear cell populations and host RNA expression.
Home sampling – A sub-group will also be invited to take samples of saliva and nasosorption between their inoculation and first follow-up visit. The first sample will be at the inoculation visit, then further samples at home (or work) at specified time points over a 48-hour period post inoculation, as outlined in the Table 2.

To ensure samples are collected within 15 minutes of the planned time participants will be asked to photograph the sample and send it electronically to the research team; for this reason, participants not familiar with smartphone technology will not be invited to take home samples. Samples will be stored with a cool pack when away from home, and in a hard-plastic box at home (preferably in a freezer if available, otherwise in a refrigerator). The participants will return the samples at their next scheduled clinic visit (Day 2 following inoculation). An additional information leaflet is provided for home samples. Participants will be reimbursed £6 per time point (post challenge) if the samples are collected as instructed, up to a total of £48.
1. Muco-ciliary clearance testing: A saccharin tablet will be inserted into the nasopharynx of a subgroup of participants. The time taken for the participant to taste the saccharin will be recorded as a measure of muco-ciliary clearance. This will be performed at day 36-57 in a sub-group of participants only.
2. Inoculation: The participant will be seated in a semi-recumbent position. Using a P200 micropipette, 0.1ml of pneumococcus-containing-fluid will be instilled into their nose. After inoculation, the participant will remain in this position for up to 15mins. The participant is given a safety pack containing:
3. Thermometer
4. Safety information leaflet
5. Study ID card with contact details
6. Amoxicillin 500mg TDS 5/7 supply OR Clarithromycin 500mg BD 5/7 supply (if penicillin allergic) including antibiotic information sheet
7. COPD participants will be provided with Prednisolone 40mg OD for 5 days during the inoculation visit including an information sheet explaining the circumstances that this can be taken

Participants are asked to contact the team daily for the first 3-4 days with their temperature recording and any symptoms before 1200hrs. Should they not make contact by the specified time, a member of the research team will contact the participant. If no contact is made, then a prior defined ‘secondary contact’ will be telephoned. During the post-inoculation period participants will have access to a 24/7 on-call telephone service until the end of the study.
We will ask participants to keep a written/electronic record of their symptoms during the first seven days using a likert scale. The aimed dose is 80000 CFU/100ul. We will allow a variation of half or double of this dose and have previously demonstrated in our dose-ranging studies that this range is safe and leads to similar colonisation outcome (rates and density recovered from the nasopharynx).

Healthy Smokers Timetable

Consent visit: A member of the research team will discuss the study involvement with you, this may be done as a group presentation. You will have the opportunity to ask questions and discuss the study directly with the researcher in private following the presentation. If you are happy to take part in the study, you will be asked to complete a questionnaire to demonstrate that you understand the study involvement before signing a consent form. We will inform your GP that you are taking part in the study.

Pre-Screen Visit: This appointment will take approximately 30-45 minutes. During the appointment the trialists will ask participants some routine questions about their medical health and will listen to their heart and lungs. This is done to make sure they are fit and well. A small (3ml) blood sample will be taken to check that they are well (less than one teaspoon). A urine sample will be taken to check for pregnancy (females only). All participants will have a urine test to check nicotine levels.
The trialists will assess the participants' breathing, the results may require them to have a breathing test, this is called a spirometry. This involves taking a deep breath and exhaling rapidly and forcefully into a machine. This technique is repeated ≥3 times to achieve an accurate result.

Screen visit: This appointment will take approximately 30 minutes. The trialists will take blood, throat swabs, nasal wash, nasal cells and a urine sample. Female patients will have a urine pregnancy test performed if ≥2 weeks since the pre-screen visit.

Inoculation visit
Nasosorption is collected. A dropper is used to put a small amount of water containing a small number of bacteria into each nostril. Usually volunteers have no symptoms afterwards. There will be a doctor or nurse available by telephone 24hours a day, 7 days a week to answer questions. The participants will be given a safety pack to keep with them throughout the study, this includes:
1. A course of antibiotics to keep with you in case you are unwell
2. Thermometer to check your temperature at home
3. Safety information sheet
4. Study contact card
The participants are asked to inform the trialists of their temperature and symptoms daily for the next 3-4 days using an app available on Android phones.

Monitoring Period
Clinic appointments on day 2, 7, 9, 14, 22* and 29 post inoculation. At each visit, a number of samples will be taken which may include throat swab (s), nasosorption, nasal wash, nasal cells and blood tests.

End of the study
Participants that are colonised with the bacteria at any timepoint will be asked to take the antibiotics from the safety pack to clear the bacteria
Amoxicillin 500mg three times per day for 5 days OR
Clarithromycin 500mg twice daily for 5 days *
Saccharin test: Optional extra visit, see below for details.

*Colonisation positive participants only

COPD Participants Timetable

Consent visit: A member of the research team will discuss the study involvement with you, this may be done as a group presentation. Participants will have the opportunity to ask questions and discuss the study directly with the researcher in private following the presentation. If they are happy to take part in the study, they will be asked to complete a questionnaire to demonstrate that they understand the study involvement before signing a consent form. The trialists will inform their GP that they are taking part in the study and request some information from their health records.

Pre-screen visit: This appointment will take approximately 30-45 minutes. During the appointment they will be asked some routine questions about their medical health and the trialists will listen to their heart and lungs. This is done to make sure they are fit and well. A small (up to 15 ml) blood sample will be taken to check that they are well (three teaspoons). A urine sample will be taken to check for pregnancy (females only). All participants will have a urine test to check nicotine levels.
The trialists will perform a breathing test called a spirometry. This involves taking a deep breath and exhaling rapidly and forcefully into a machine. This technique is repeated ≥3 times to achieve an accurate result. The participants will then be given an inhaler called salbutamol (blue inhaler) through a spacer device, 4 puffs are given. The breathing test is then repeated as described above 15 minutes after the inhaler. This test is used to confirm the diagnosis and severity of their COPD.
The trialists will also perform an ECG test, this measures the electrical activity of the heart and involves putting sticky electrodes across the chest, arms and legs.

Screen visit: This appointment will take approximately 30 minutes. The trialists will take blood, throat swabs, nasal wash, nasal cells and a urine sample. Female patients will have a urine pregnancy test performed if ≥2 weeks since the pre-screen visit.

Inoculation Visit
Nasosorption is collected. A dropper is used to put a small amount of water containing a small number of bacteria into each nostril. Usually volunteers have no symptoms afterwards. There will be a doctor or nurse available by telephone 24 hours a day, 7 days a week to answer questions. The participants will be given a safety pack to keep with them throughout the study, this includes:
1. A course of antibiotics to keep with you in case you are unwell
2. A course of Prednisolone to keep with you in case you are unwell
3. Thermometer to check your temperature at home
4. Safety information sheet
5. Study contact card
The participants are asked to inform the trialists of their temperature and symptoms daily for the next 3-4 days using an app available on Android phones.

Monitoring Period
Clinic appointments on day 2, 7, 9, 14, 22* and 29 post inoculation. At each visit, a number of samples will be taken which may include throat swab (s), nasosorption, nasal wash, nasal cells and blood tests

End of the study
Participants that are colonised with the bacteria at any time point will be asked to take the antibiotics from the safety pack to clear the bacteria
Amoxicillin 500mg three times per day for 5 days OR
Clarithromycin 500mg twice daily for 5 days *
Saccharin test: Optional extra visit see below for details.

Phone call follow up: A member of the research team will contact participants by phone to ask about their COPD and any exacerbations following the study.
*Colonisation positive participants only

Intervention Type
Other

Primary outcome(s)
Colonisation of SPN6 post inoculation; Timepoint(s): At any timepoint post inoculation

Key secondary outcome(s))
1. The presence of pneumococcal bacteria in nasal wash, detected by classical microbiological and molecular methods at any timepoint post challenge
2. Cell populations and counts measured using flow cytometry from nasal samples pre and post challenge
3. Antibody levels measured in serum and nasal wash samples pre and post challenge
4. The pneumococcal killing will be measured by counting the recovered pneumococcal bacteria following incubation with the neutrophils compared to bacteria that were not incubated with neutrophils
5. Daily symptoms will be recorded using a Likert scale for 7 days post challenge

Completion date
02/09/2023

Eligibility

Key inclusion criteria
Inclusion criteria for healthy cigarette smokers:
1. Adults aged 18 - 50 years
2. Current regular cigarette smoker - smoking a mean average ≥5 cigarettes per day for the preceding 3 months
3. Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement
4. Access to telephone (safety and timely communication)
5. Capacity to give informed consent

Inclusion criteria for COPD patients:
1. Adults aged 50 - 84 years
2. Either a current regular cigarette smoker - smoking a mean average ≥5 cigarettes per day for the preceding 3 months (SMOKER) or an ex-smoker - no regular e-cigarette, vaping or cigarette smoking in the preceding 3 months
3. Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement
4. Access to telephone (safety and timely communication)
5. Diagnosis of COPD defined by Spirometry as FEV1/FVC ratio < 0.7 (post bronchodilator)
6. Capacity to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Exclusion criteria for Group 1 and 2:
1. In a caring role or with intimate physical contact with at-risk individuals (children under 5yrs, immunosuppressed adults) during the period of pneumococcal colonisation
2. History of or current regular drug or alcohol abuse (frequently drinking alcohol: men and women should not regularly drink > 3-4 units/day and > 2-3 units/day respectively)
3. Taking daily medications that may affect the immune system e.g. systemic steroids, systemic corticosteroids, antibiotics, or disease-modifying anti-rheumatoid drugs
4. Any acute illness (new symptoms within preceding 14 days which are unexplained by the known past medical history)
5. Having received any antibiotics in the preceding 28 days
6. History of culture-proven pneumococcal disease
7. Involved in another clinical trial unless observational or in follow-up (non-interventional) phase
8. Have been involved in a clinical trial involving EHPC and bacterial inoculation in the past three years
9. Disease associated with altered immunity, including diabetes, alcohol abuse, malignancy, rheumatological conditions
10. At the clinician's discretion any unstable or poorly controlled co-morbidity
11. Taking medication that affects blood clotting (except aspirin and clopidogrel) e.g. warfarin or other oral or injectable anticoagulants
12. Have any uncontrolled medical/ surgical conditions such as but not restricted to: hypertension, mental health conditions, epilepsy, narcolepsy, chronic conditions requiring pain medication such as osteoarthritis, skin conditions, allergies, hay fever, and any other condition at the discretion of the PI
13. Allergy to penicillin/amoxicillin AND clarithromycin
14. Concern of the study doctor about the participant's health

Exclusion criteria for healthy cigarette smokers:
1. > = 20 pack year smoking history

Exclusion criteria for COPD patients:
1. < 20 pack year smoking history
2. Severe COPD (post bronchodilator FEV1/FVC < 0.7 AND FEV1 < 50% predicted post bronchodilator)
3. Reversibility of > 15% of the baseline FEV1 suggests a diagnosis of asthma and would lead to exclusion from the study
4. Acute exacerbation of COPD in the last 3 months or more than 3 exacerbations in the last 12 months requiring oral steroids and/or hospitalisation

5. On ambulatory or long-term oxygen therapy
6. Significant cardiorespiratory disease, other than COPD (excluding stable hypertension)
7. Definite diagnosis of pre-existing asthma (excluding childhood asthma)

Date of first enrolment
18/09/2018

Date of final enrolment
02/10/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Accelerator Research Clinic
Liverpool Life Sciences Accelerator Building
1 Daulby Street
Liverpool
United Kingdom
L7 8XZ

Sponsor information

Organisation
Liverpool School of Tropical Medicine (LSTM)

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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. Data requests should be submitted to the EHPC coordinator (Catherine.Molloy@lstmed.ac.uk); these are considered by the program leads, and will be subject to data transfer agreements and ethical review if necessary.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version V2.1	10/09/2018	27/09/2018	No	Yes
Participant information sheet	version V2.1	10/09/2018	27/09/2018	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes