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Biomarkers in respiratory immunology

Submission date 29/10/2018	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 21/11/2018	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 25/09/2024	**Condition category** Respiratory	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study primarily focuses on a type of bacteria called pneumococcus. This bacteria is the most common cause of pneumonia. In this study, bronchoscopic (camera tests into the lungs) data will be collected from participants with healthy lungs and also those with respiratory diseases. Bronchoscopy is a useful and well-tolerated research method. When studying respiratory diseases obtaining lung/lower respiratory tract cells, rather than just blood cells, is increasingly accepted as best research practice.
When performing bronchoscopy, fluid can be instilled into the lungs and withdrawn with manual hand-held suction – this is called research bronchoalveolar lavage (BAL). This enables the removal of lung cells and lung lining fluid from the lung mucosal surface. BAL has assumed a more prominent role in diagnosis and management of lung disease, and hopefully in the future as a prognostic tool.
This study aims to use research bronchoscopy and BAL to collect immune and clinical data for the exploration of different respiratory biomarkers (indicators of disease) that correlate with lung infection and protection, and the impact of ageing on the immune system in the lungs.

Who can participate?
1. Healthy adult males and non-pregnant females
2. Adults with respiratory disease, including asthma, COPD, pulmonary fibrosis, bronchiestasis, recent pneumonia or lower respiratory tract infection

What does the study involve?
Participants will undergo several upper respiratory tract investigations:
1. Nasosorption, where a small piece of blotting paper is placed inside the nostril and held there for up to 3 minutes
2. Nasal wash, where a little salty water is gently squirted into the nose and the water is collected as it runs out
3. Nasal swab - a cotton swab is inserted gently into the nose
4. Nasal cells, collected from the inner surface of the nostril using a very thin plastic spoon
5. Throat swab - a small cotton swab is used to wipe the back of the throat
All participants will undergo a bronchoscopy as a day procedure at the hospital, with local anaesthetic and if required, sedation. The preparation time will take around 15-20 minute and the procedure itself will take around 7-15 minutes. Participants will be observed for at least 2 hours following bronchoscopy. During this procedure, blotting paper will be passed down the

bronchoscope, similarly to the nasosorption procedure. Bronchoalveolar lavage (BAL) will also be performed as part of the bronchoscopy. Saline solution (around the same amount as a cup of tea) will be introduced to the lung and then withdrawn using gentle suction. Bronchial brushing involves a small brush being passed down the bronchoscope to obtain a cell sample from the lung lining.
All participants will have blood samples taken at their screening/consent visit and at their bronchoscopy visit.
All participants will be asked to telephone the research team the day after the bronchoscopy to inform them of any problems, provide feedback and check participants are feeling well.
Occasionally participants will be invited for a clinical follow up with the research team. This will involve a clinical exam, asking a few questions about symptoms and monitoring vital signs (heart rate, blood pressure and temperature)

What are the possible benefits and risks of participating?
There is no immediate benefit to the participants; however, they will be reimbursed for their time and involvement.
The risks associated with blood sampling and cannulation are minimal, but this may cause temporary pain, bruising and/or bleeding to the arm. Blood sampling and cannula insertion will be performed by trained medical professionals.
Bronchoscopy is classed as a safe procedure, which carries little risk. Most people do not suffer any ill effects but of those that do, the common side effects are a sore throat and hoarseness for a few hours, or perhaps nasal discomfort and a cough after. Therefore, all participants are observed for at least two hours after bronchoscopy. It is possible that participants will experience a drop-in blood oxygen levels or breathlessness during the procedure and if these occur, the procedure may be stopped. Up to 25% of people experience mild right sided chest pain with mild fever) for some hours during the evening/night, following the procedure. Major complications would include breathing difficulties (from sedative medication or temporary blockage of the airway), abnormal heart rhythm and infection.
The risks associated with bronchial brushing and bronchosorption are minimal. Bronchial brushing can cause minor bleeding. During bronchosorption, the blotting paper could dislodge from the wire/catheter, this would be retrieved using biopsy forceps at the time of the bronchoscopy or may be spontaneously coughed up after the bronchoscopy itself. This risk is reduced by screening participants and checking clinical bloods prior to the procedure and with the bronchoscopy being performed by a highly trained specialist team.
There is limited risk associated with taking upper respiratory samples. During a nasal wash, participants may swallow a small amount of salty water however this is harmless. The throat swab may make you gag a little. The nasal swab can be a little uncomfortable (this passes very quickly) and may cause a small amount of bleeding, but this is uncommon. The nasosorption can tickle the nose a little. The nasal cell sample is slightly uncomfortable and may make your eyes water, this is very momentary. Sometimes a small amount of blood can be evident on the sample probe; however, it is highly unusual for it to cause an actual nose bleed.

Where is the study run from?
The study is run from the Liverpool School of Tropical Medicine Accelerator Research Clinic (UK). Clinic visits and assessment will occur here. The exception is the bronchoscopy procedure, which will be undertaken in the Royal Liverpool University Hospital (UK)

When is the study starting and how long is it expected to run for?
September 2018 to November 2028

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

Who is the main contact?
Angie Hyder-Wright
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Study website
https://www.lstmed.ac.uk/pneumoniavaccine

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Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
248333

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 39473, IRAS 248333

Study information

Scientific Title
A study of bronchoscopic biomarkers in respiratory immunology

Study objectives
Research bronchoscopy can be used to investigate lung biomarkers to evaluate responses to bacterial/viral aspiration in healthy participants and different patient groups with respiratory colonisation/infection.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 31/08/2018, North West - Liverpool East REC (3rd Floor Barlow House HRA NRES Centre, Manchester, M1 3DZ, United Kingdom; +44 (0)2071048001; liverpooleast.rec@hra.nhs.uk), ref: 18/NW/0582

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Respiratory infection and inflammation

Interventions
Participants will attend a bronchoscopy appointment. Fibreoptic bronchoscopy will be performed via a nasal or oral route using a standard operating procedure. Participants will fast for at least 4 hours prior to bronchoscopy. Bronchoabsorption, bronchoalveolar lavage and bronchial brushing will be performed as part of the bronchoscopy.
Bronchoabsorption will be used to collect epithelial lining fluid, which will then be analysed for biomarkers of respiratory infection and inflammation. Bronchoalveolar lavage will be used to analyse bronchoalveolar fluid for cell counts, differential and volume yield and other biomarkers of respiratory infection and inflammation. Bronchial brushing will be used to collect samples for RNA and mitochondrial DNA analysis.
Blood samples will also be taken at the bronchoscopy visit, along with at their screening/consent visit.
Participants will be followed up 1-10 days after the bronchoscopy with a telephone or clinic consultation to confirm no adverse events (AEs) or serious adverse events (SAEs) have arisen and ensure recovery. After a telephone follow-up a participant may be asked to also attend clinic for a full physical assessment if deemed necessary by the investigator. A 24-hour on-call emergency telephone number will be available to participants should they require medical advice.

Intervention Type
Other

Primary outcome measure
Immune responses in the lungs of healthy participants compared to different patient groups, assessed by bronchoalveolar lavage (BAL) and blood using lung biomarker levels at the time of bronchoscopic sampling.
Since this is an exploratory study the precise methods of measurement will be defined after the initial 50 study participants samples have been taken.

Secondary outcome measures

Since this is an exploratory study the precise methods of measurement will be defined after the initial 50 study participants samples have been taken, and re-defined as required.
1. Bacterial/viral aspiration in the lung, assessed by bronchoalveolar lavage (BAL) using classical microbiological/virological techniques on samples taken at screening and at the time of bronchoscopic sampling
2. Biomarkers of respiratory colonisation, assessed by laboratory analysis on samples taken at screening and at the time of bronchoscopic sampling
3. Effectiveness of bronchoabsorption technique to assess inflammation and infection in healthy participants and different patient groups, assessed by laboratory analysis on samples taken at the time of bronchoscopic sampling
4. Upper and lower airway microbiome in healthy participants and different patient groups, assessed using laboratory techniques at screening and at the time of bronchoscopic sampling
5. Opsonophagocytic bacterial killing activity (OPKA) in healthy participants and different patient groups, assessed using laboratory OPKA assays on samples taken at screening and at the time of bronchoscopic sampling
6. Bacterial and viral specific immune responses in the lung, assessed using laboratory assays on samples taken at screening and at the time of bronchoscopic sampling

Overall study start date
01/09/2018

Completion date
01/11/2028

Eligibility

Key inclusion criteria
1. Capacity to provide written consent before any study procedures are performed and can understand and comply with the requirements of the study.
2. Males and non-pregnant females
3. Aged 18-85 years
4. Fluent in English, able to understand the procedures and convey any adverse events effectively to the research team

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
85 Years

Sex
Both

Target number of participants
Planned Sample Size: 500; UK Sample Size: 500

Key exclusion criteria
Any of the following will exclude participants from the study:
1. Uncontrolled medical or surgical conditions that may preclude nasal or oral intubation with a bronchoscope or the bronchoscopy itself, in the opinion of the investigator
2. Any report of acute illness or febrile event that has not resolved 72 hours before bronchoscopy
3. Previous adverse reactions to benzodiazepines or anaesthetic agents (lidocaine) including reversal agents such as flumazenil
4. Participated (taken investigative drug and/or device) in another clinical trial within 1 month or within drug's 5 half-lives, whichever is longer, before the study procedure (this is not relevant to participants in an EHPC study)
5. Full blood count, clotting or renal function level outside of normal range and deemed as clinically significant by the investigator
6. Very poor venous access
7. Not abstained from alcoholic beverages or alcohol-containing products for at least 24 hours before bronchoscopy
8. Receipt of blood products within 2 months prior to screening
9. Should not participate in this study for their own safety in the opinion of the Investigator (or designee)

Exclusion criteria for participants with acute or chronic respiratory disease such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, pneumonia or lower respiratory tract infection:
1. Unable to perform spirometry (spirometry must be within 6 months prior to screening)
2. On long term oxygen therapy (LTOT)
3. Oxygen saturations on screening of <92% on air
4. Any uncontrolled medical or surgical condition as deemed clinically significant by the CI

Date of first enrolment
15/09/2019

Date of final enrolment
02/09/2028

Locations

Countries of recruitment
England

United Kingdom

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Sponsor type

University/education

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Government

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

Results and Publications

Publication and dissemination plan
We plan to publish in a high-impact peer-reviewed journal (open access where possible). Data will also be presented at appropriate local, national and international conferences. In addition, we will produce lay reports of our findings which will be made available to all participants.

Intention to publish date
01/11/2029

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