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Defining how antibiotics disrupt lung immune responses in asthma and health

Submission date
13/06/2025

Recruitment status
Not yet recruiting

Registration date
18/06/2025

Overall study status
Ongoing

Last Edited
13/06/2025

Condition category
Other

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

Plain English summary of protocol

Background and study aims
This is a trial designed to help us better understand how changes in the bacteria that live in everyone's lungs and gut affect inflammation in the lungs, particularly in asthma.
We will find this out by looking at how both things change before and after participants take a common antibiotic medicine called amoxicillin.
We are looking at these changes in people both with and without asthma. We are interested in whether any changes antibiotics cause are bigger and more significant in people who have asthma, and the potential impact for how people with asthma are treated with antibiotics in the future.
When antibiotics are used, they don't just kill the bacteria causing an infection – they will also reduce the number of normal bacteria that usually live in the body, causing no harm.
We are interested in whether changing your population of healthy bacteria (with antibiotics), especially in the gut where the vast majority live, changes the type of inflammation in the lungs. If it does, this would be a reason for doctors to be more careful when prescribing them. Especially as we also know many simple infections would have gotten better on their own without antibiotics. We are using amoxicillin in this trial as it is one of the most common antibiotics.

Who can participate?
Adults aged 18 to 80 years old, in generally good health, with and without mild asthma.

What does the study involve?
The study involves answering health questionnaires and assessment of lung function, followed by two bronchoscopy procedures where samples of lung fluid will be taken. Bronchoscopy involves the use of a camera at the end of a very narrow flexible tube (usually inserted through the nose) to look at the lungs. The narrow tube also has a suction port to take fluid samples. Between the procedures a course of amoxicillin or an inactive placebo tablet is taken. Participants will also provide stool samples and have blood taken at the two procedure visits and at intervals over 1 year afterwards.

What are the possible benefits and risks of participating?
There are no expected direct health benefits to participants.

There are risks associated with antibiotics (allergy, nausea, diarrhoea). There are risks associated with bronchoscopy, including but not limited to: discomfort during the procedure; coughing, during and immediately afterwards; temporary low oxygen levels; wheeze; nose bleeds; fainting. Sedation used for bronchoscopy may cause nausea, vomiting, or lightheadedness.
There are some more serious risks associated with bronchoscopy, such as pneumothorax (air trapped in the chest), bleeding in the lungs and death. All these complications are very rare (risks of 1:1000 or lower). Sedation can rarely cause a depressed breathing rate or low blood pressure. We are only including participants who have no medical conditions or history which would increase their individual risk of serious complications from bronchoscopy or sedation.

Where is the study run from?
The study will run at the Manchester Clinical Research Facility and the North-West Lung Centre at Wythenshawe Hospital (UK)

When is the study starting and how long is it expected to run for?
November 2024 to November 2027

Who is the main funder?
The Medical Research Council through an Experimental Medicine Grant (Grant Code: MR /Y008812/1) (UK)

Who is the main study contact?
Prof Tim Felton, Tim.felton@manchester.ac.uk

Study website
https://research.cmft.nhs.uk/facilities-services/nihr-centre-for-precision-approaches-to-combatting-antimicrobial-resistance/projects

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
354874

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Grant Code: MR/Y008812/1

Study information

Scientific Title
Defining mechanisms underpinning antibiotic mediated disruption of pulmonary immune responses

Acronym
DEMAND

Study objectives
A causal link between disruption of the human microbiome and type two inflammation in the lungs exists - and is of different character and/or magnitude in healthy volunteers and asthmatics.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted, Ethics committee name not provided (Address not provided, City not provided, Zip/postal code not provided; Telephone number not provided; Email not provided), ref: Reference number not provided

Study design
Single-centre interventional double-blinded randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Other

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

Health condition(s) or problem(s) studied
Influence of microbiome disruption on expressed immune phenotype in health and in asthma

Interventions
Two cohorts: healthy volunteers (n = 34), asthmatics (n = 34). Total participants n = 68.
Within each cohort, participants are randomised using double-blinded sequential block randomisation to ensure equal allocations to one of two interventions:
1. Amoxicillin 500 mg, three times daily, 7 days
2. Visually matched inactive placebo, three times daily, 7 days

The study involves answering health questionnaires and assessment of lung function, followed by two bronchoscopy procedures where samples of lung fluid will be taken. Bronchoscopy involves the use of a camera at the end of a very narrow flexible tube (usually inserted through the nose) to look at the lungs. The narrow tube also has a suction port to take fluid samples. Between the procedures a course of amoxicillin or an inactive placebo tablet is taken. Participants will also provide stool samples and have blood taken at the two procedure visits and at intervals over 1 year afterwards.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Amoxicillin

Primary outcome measure
1. In-depth immune cell characterisation to quantify the degree of expression of interleukins and immune cell surface markers associated with type 2 inflammation in paired broncho-alveolar fluid (BAL) and blood at baseline (day 0) and post-intervention (day 7)
2. Matched to fraction of exhaled nitric oxide (FeNO) measurements (in parts per billion [ppb]) at baseline (day 0) and post-intervention (day 7)
3. Blood immune cell characterisation to quantify the degree of expression of interleukins and immune cell surface markers associated with type 2 inflammation will be repeated at follow-up at approximately 6, 12, 26 and 52 weeks post-intervention
4. FeNO measurements (ppb) will be repeated at follow-up at approximately 6, 12, 26 and 52 weeks post-intervention

Secondary outcome measures
1. Characterisation of the gut bacterial microbiome composition pre- and post-intervention (day 0 and day 7) by microbiome sequencing techniques performed on paired BAL and stool samples,

including analysis of the change in microbiota attributable to antibiotic administration
2. Assessment of the recovery of the gut microbiome over the following year through serial microbiome sequencing on stool samples at approximately 6, 12, 26 and 52 weeks post-intervention
3. Quantification and characterisation of stool and blood bacterial metabolites by short chain fatty acid assay at baseline (day 0), post-intervention (day 7) and at approximately 6, 12, 26 and 52 weeks post-intervention

Overall study start date
06/11/2024

Completion date
02/11/2027

Eligibility

Key inclusion criteria
1. Males and Females
2. Mild asthma patients aged between 18 and 80 years, inclusive
3. Healthy volunteers aged between 18 and 80 years, inclusive
4. Non-smokers or Ex-smokers with fewer than 10 pack years and >6 months abstinence
5. Healthy volunteers: no clinically relevant abnormalities based on history, examination, vital signs, and no history of respiratory disease
6. Asthma cohort participants only: confirmed airway responsiveness via methacholine challenge at screening visit
7. Asthma cohort participants only: good or partial symptom control according to GINA classification and corticosteroid naïve
8. Capacity to consent

Participant type(s)
Healthy volunteer, Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
68

Key exclusion criteria
1. Have received any systemic antibiotic medication:
1.1. To treat an infection arising during the participant’s potential study participation

1.2. Within the year prior to potential inclusion
2. Have received any topical or systemic treatment for oral thrush in the year prior to inclusion.
3. Have received any leukotriene antagonist medication within the year prior to the inclusion.
4. History of hypersensitivity or allergy to penicillins or other beta-lactam antibiotics.
5. Treatment for asthma beyond intermittent inhaled salbutamol use– i.e. regular inhaled corticosteroids or above or any use of systemic or inhaled corticosteroids - during or within one year prior to inclusion in the study
6. Baseline FEV1 <70% (asthma cohort) or <80% (healthy volunteers).
7. Current smokers or ex-smokers with over 10 pack years or under 6 months abstinence.
8. Current regular smokers (over once a month) of cannabis or other illicit drugs.
9. Conditions or medications that may affect the safety of bronchoscopy, sedation, amoxicillin administration, or have an independent effect on airway immune responses and reactivity: a. any pulmonary or chest wall disease other than asthma (including but not limited to chronic obstructive pulmonary disease, interstitial lung disease, significant chest wall deformities); b. other disease states that increase the risk of hypoxaemia, or the risk of serious sequalae of hypoxaemia; c. regular use of anti-histamine medications – unless participant able to discontinue during bronchoscopy phase of the study; d. regular anticoagulant therapy; e. upper or lower respiratory tract infection within 4 weeks prior to enrolment; f. history of adverse reactions to sedative or anaesthetic agents beyond expected side effects.
10. Conditions or medications that have an independent effect on the host gut or respiratory flora and microbiome (including but not limited to inflammatory bowel disease, irritable bowel syndrome, small intestinal bacterial overgrowth)
11. Pregnant
12. Other severe, acute or chronic, medical or psychiatric conditions that may increase the risk associated with trial participation or interfere with the interpretation of trial results.
13. Inability to collect and provide a stool sample.
14. Participation in other interventional research trials within the study period – except where appropriate cross-enrolment has been agreed by both Chief Investigators.

Date of first enrolment
01/09/2025

Date of final enrolment
03/11/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Sponsor information

Organisation
University of Manchester

Sponsor details
Research Governance, Ethics and Integrity Team (Clinical Trials)
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Sponsor type
University/education

Website
https://www.manchester.ac.uk/research/environment/governance/clinical-trials-medical-devices/

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

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

Publication and dissemination plan
At the completion of the study the data generated will be analysed and prepared as a manuscript (s) for publication. Decisions on rights to publish the study data are limited to the study leadership team. This manuscript(s) will be published in a high-impact, open-access scientific journal(s). This will allow for unrestricted access to the study's results for both the wider academic community and lay study participants. In addition, the study participants will be made aware of publication(s) through a newsletter that summarises the key findings for a lay audience.

Intention to publish date
01/11/2027

Individual participant data (IPD) sharing plan
Anonymised transcriptomic, immunological, metagenomic and metabolomic datasets, alongside anonymised study metadata, will be made publicly available via long-term storage in suitable repositories. This will be made available approximately 12 months after the study conclusion. Access to these public repositories is unrestricted.
Decisions on earlier access of research data to new users will be made by the study leadership team and documented for subsequent independent review. An external independent advisor will be identified to periodically review the outcomes of access requests.
Datasets will be available via the University of Manchester Pure research information repository (http://www.staffnet.manchester.ac.uk/pure/).
Participants will be consented for this data sharing at the outset of their involvement in the study.

IPD sharing plan summary
Stored in publicly available repository