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Mechanism of early tissue responses in vaccination with mRNA vaccines

Submission date 04/07/2025	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 17/07/2025	**Overall study status** Ongoing	
Last Edited 17/07/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
Older adults and individuals taking specific immunosuppressive medications, such as those used to treat inflammatory bowel disease (IBD), may not respond as effectively to mRNA vaccines. This study aims to understand the underlying reasons by examining samples taken directly from the lymph nodes in the armpit after administration of an mRNA vaccine. These samples will be compared with those from younger adults not receiving immunosuppressive therapies. The goal is to inform the development of improved vaccines, particularly for populations with the greatest need, such as older adults and individuals with immune conditions. Lymph nodes, which are bean-shaped organs, play a crucial role in generating immune cells following vaccination. Using ultrasound scanning, researchers can collect cells from these lymph nodes to observe how the immune system responds to an mRNA vaccine. This procedure, known as ultrasound-guided fine needle aspiration (FNA), is commonly used in clinical settings. The study will investigate lymph node responses in three groups: younger adults, older adults, and individuals receiving anti-tumour necrosis factor (TNF) therapy, all of whom will receive a licensed COVID-19 mRNA vaccine.

Who can participate?
Healthy volunteers and patients, divided into three groups:
- 15 individuals aged 18–45 years
- 15 individuals aged 65 years or older
- 15 individuals aged 18–50 years who are receiving anti-TNF therapy

What does the study involve?
Participants will receive a licensed COVID-19 mRNA vaccine, followed by a seasonal influenza vaccine administered four weeks later. Fine needle aspiration (FNA) will be performed on both armpits at 14 days and 112 days after the mRNA vaccine. An optional FNA may be conducted at day 56.

Eligibility will be assessed during a screening visit. Those who qualify will attend up to six additional visits over 24 weeks. Blood samples will be collected at each visit.

What are the possible benefits and risks of participating?
The study may contribute to the development of more effective vaccines for vulnerable populations. The FNA procedure used to collect immune cells is standard in clinical practice. As with any medical procedure, there may be minor risks such as bruising or discomfort.

Where is the study run from?
Oxford Vaccine Group, Oxford, UK

When is the study starting and how long is it expected to run for?
May 2025 to February 2028

Who is funding the study?
1. UK Research and Innovation (UKRI)
2. Medical Research Council (MRC)

Who is the main contact?
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Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
347668

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 64039

Study information

Scientific Title
An experimental medicine study of early tissue response in vaccination with lipid-encapsulated non-amplifying mRNA in Lymph nodE single-cell Genomics in AnCestrY and ageing (LEGACY MechRNA)

Acronym
MechRNA LEGACY04

Study objectives
Principal research question/objective
To measure the lymph node germinal centre response to mRNA vaccination in people on anti-TNF therapy and compare that with healthy adults.

Secondary research questions/objective
To measure the lymph node response to mRNA vaccination in younger adults versus older people and to identify key cellular processes that are disrupted, leading to an impaired humoral response.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 19/06/2025, North West - Haydock Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)2071048138, 207 104 8131, 2071048117; haydock.rec@hra.nhs.uk), ref: 25/NW/0164

Study design
Non-randomized open-label experimental medicine study

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Why mRNA vaccines do not appear to work as well in older adults and people on specific immunosuppressive medications, such as those for inflammatory bowel disease (IBD)

Interventions
This is an open-label, observational, experimental medicine study to investigate human immune responses in lymph node cells after immunisation with the COVID-19 mRNA booster vaccine. Participants will be adults in three groups: 18-45 years, ≥65 years, and 18-50 years on anti-TNF therapy. Participants will also receive the seasonal influenza vaccine separately, 4 weeks after the COVID-19 mRNA vaccine.

All participants will receive a single dose of each vaccine separately as described above. All participants will have a fine needle aspiration (FNA) biopsy of axillary lymph nodes at 14 days and 112 days after COVID-19 mRNA vaccination. An optional, additional FNA will also be offered to participants and will be conducted 42 days after COVID-19 mRNA vaccination.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
COVID-19 mRNA vaccine

Primary outcome(s)
The frequency of GC B cells in the ipsilateral and contralateral LNs post mRNA immunisation in younger adult volunteers compared with those on anti-TNF therapy using single-cell ribonucleic acid sequencing 5-prime (5’ scRNA-seq) at day 14

Key secondary outcome(s))
The frequency of GC B cells in the draining LN post-mRNA immunisation in older people versus healthy controls or individuals on anti-TNF therapy, and the cell signalling pathways active in these cells using single-cell ribonucleic acid sequencing 5-prime (5’ scRNA-seq) at day 14

Completion date
28/02/2028

Eligibility

Key inclusion criteria
Participants must satisfy all the following criteria to be eligible for the study:
1. Adults aged between 18 to 45 years (inclusive) OR aged 65 years and over OR aged 18 to 50 years on anti-TNF immunosuppressive therapy
2. Medically stable (i.e., according to investigator judgement, it is not anticipated that the

participant will require hospitalisation within the study period or that they will need to withdraw from the study for medical reasons before completion of protocol-specified follow-up). A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalisation for worsening disease during the 90 days prior to enrolment.
3. Able to attend the scheduled visits and comply with all study procedures
4. Willing and able to give informed consent for participation in the study
5. Agree to allow study staff to contact his or her GP or equivalent NHS databases to access the participant's vaccination records, medical history
6. Willing to allow their GP and/or consultant, if appropriate, to be notified of participation in the study
7. Willing to provide their national insurance number or passport number to be registered on The Over-Volunteering Prevention System (TOPS)
8. Agree to refrain from blood donation whilst in the study
9. For participants of childbearing potential only (as defined by protocol Section 8.5): not planning pregnancy during participation in the study and willing to have a negative pregnancy test on the days of screening and study injections
10. Have received at least a primary (two-dose) schedule of any MHRA, UK-authorised or licensed COVID-19 vaccine

For Group C participants (participants taking anti-TNF therapy), they would also have to satisfy the following criteria in addition to the above to be eligible for the study:
11. Have a diagnosis of inflammatory bowel disease (Crohn's disease, ulcerative colitis, or inflammatory bowel disease unclassified)
12. On stable anti-TNF immunosuppressive therapy for the preceding 12 months before enrolment

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Participation in another research study involving an investigational product, the receipt or planned receipt of an investigational product, or the donation of significant volumes of blood that could compromise the integrity of this study, either within the 12 weeks prior to enrolment or planned during the study period.
2. Body mass index ≥35
3. Administration of immunoglobulins and/or any blood products within the three months of study enrolment.
4. Administration of regular anticoagulation medication likely to induce bruising or bleeding on fine needle aspiration.

5. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; severe infection(s); receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months, or long-term systemic corticosteroid therapy (including for more than 7 consecutive days within the previous 3 months).
6. History of anaphylaxis in relation to vaccination, or local anaesthetic such as lidocaine.
7. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine including hypersensitivity to the active substance or to any of the excipients of the vaccine or to local anaesthetic such as lidocaine.
8. History of cancer that is not resolved (except basal cell carcinoma of the skin and cervical carcinoma in situ).
9. History of any serious psychiatric condition likely to affect participation in the study.
10. For participants of childbearing potential only: participants who are pregnant, breastfeeding or lactating, or are planning pregnancy during the study.
11. History of a bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, or neurological illness, as judged by the Investigator (note, mild/moderate well-controlled co-morbidities are acceptable).
13. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units per week.
14. Suspected or known injecting drug use within the 5 years preceding enrolment.
15. Detectable circulating hepatitis B surface antigen (HBsAg).
16. Seropositive for hepatitis C virus (antibodies to HCV).
17. Seropositive for HIV.
18. A history of pericarditis, myocarditis or other cardiac inflammation deemed significant by the investigator.
19. Any clinically significant finding on screening investigations, that are either unlikely to resolve or do not resolve on repeat testing (at the discretion of an Investigator) within the recruitment timeline of the study.
20. Member of the study team. This is deliberately loosely defined, but at a minimum will include: anyone on the delegation log; anyone who might be anticipated to be placed onto the delegation log in the course of the study; anyone who has access to personal data on study participants (beyond name, contact details, DOB); and anyone who attends meetings where details of the study are discussed, for example safety updates.
21. Any confirmed or suspected immunodeficient state unrelated to anti-TNF therapy, including HIV infection; asplenia; anti-cancer chemotherapy or radiation therapy within the preceding 12 months, or long-term systemic corticosteroid therapy (including for more than 7 consecutive days within the previous 3 months).
22. Participants taking any other systemic immunomodulator apart from / concurrently with anti-TNF immunosuppressive therapy.
23. Any evidence of known inflammatory disease episode while on anti-TNF immunosuppressive therapy within a 12-month period.

Date of first enrolment
21/07/2025

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
Paediatrics, Oxford Vaccine Group, Headington
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Study participating centre
John Radcliffe Hospital
Headley Way
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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?
Participant information sheet	Participant information sheet version 1.1	11/11/2025	11/11/2025	No	Yes
Protocol file		16/06/2025	04/07/2025	No	No