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Examining lymph node cells to assess how age affects immune responses

Submission date
27/08/2024

Recruitment status
No longer recruiting

Registration date
10/09/2024

Overall study status
Ongoing

Last Edited
18/07/2025

Condition category
Infections and Infestations

[X] 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
Older people are at risk of severe disease from pathogens with pandemic potential. The adult population aged 65 years and over was the largest vulnerable patient group during the COVID-19 pandemic. This population continues to grow, increasing the at-risk patient population facing any future pandemic. Age-related immune decline, comorbidity and risk of exposure to infection in health and social care facilities all contribute to this risk. Vaccines are the major tool to protect against this but suffer from a lack of efficacy in older people. This is because the immunogens are not designed with the ageing immune system in mind. The World Health Organisation (WHO) has prioritised twelve diseases for pandemic research and development; second on the list after COVID-19 is Crimean-Congo haemorrhagic fever (CCHF). This is a tick-borne viral haemorrhagic fever that can also be transmitted during animal slaughter and through human-to-human transmission. Based on its risk to public health, epidemic potential and inadequacy of countermeasures. It is listed as a high-consequence infectious disease by the UK Health Security Agency (UKHSA). As the host tick is not distributed in the UK, younger and older adults entering the study are not expected to have any previous immunity. This provides a relevant model for studying immune priming and boosting in older adults who are vulnerable to severe infectious diseases. This study will compare the lymph node responses of younger and older adults with the response in the blood, using a novel immunogen (ChAdOx2 CCHF) to stimulate the immune response.

Who can participate?
Healthy adults in two age groups: 18-45 and ≥65 years old

What does the study involve?
All participants will receive two doses of ChAdOx2 CCHF, 12 weeks apart. Lymph node samples using fine needle aspiration (FNA) will be taken from both armpits on three occasions. Inside the lymph nodes are cells that make antibody responses to vaccines, and it is this response that we want to measure. Each study visit will consist of a blood draw and collection of information on serious adverse events. In addition to visits, participants will be asked to complete a short diary for 7 days after each study injection.

What are the possible benefits and risks of participating?
By participating in this study, participants will not directly receive any personal health benefits from the study or its procedures. However, they will be helping us to understand how immune responses to immunisation change with ageing. No specific additional medical care will be provided through participation, and medical procedures will be performed to determine eligibility and safety during the study.
The risks are limited to localised bruising and discomfort occurring at the site of blood sampling and fine needle aspiration of lymph nodes. After injection with immunogen, short-lived symptoms may occur, such as fever and discomfort in the arm. The study injection has been made using similar technology to the Oxford-AstraZeneca COVID-19 vaccine, which has been associated with rare disorders including abnormal blood clotting.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
August 2024 to July 2026

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

Who is the main contact?
Nelly Owino, nelly.owino@paediatrics.ox.ac.uk

Study website
https://www.ovg.ox.ac.uk/studies/legacy02

Contact information

Type(s)
Scientific, Principal Investigator

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Type(s)
Public

Contact name

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
327998

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Medical Research Council (MRC) Grant Code: MR/W024977/1, CPMS 56121, IRAS 327998

Study information

Scientific Title
An experimental medicine study of Crimean–Congo haemorrhagic fever (CCHF) vaccine immune challenge responses in Lymph nodE single-cell Genomics in AnCestrY and ageing (LEGACY02)

Acronym
LEGACY02

Study objectives
This study aims to understand how immune cells in lymph nodes respond to a new immunisation and how this response changes with ageing. This information will help design future vaccines (for example, for future pandemics) and tailor vaccination strategies in different patient populations, including older people.

Older people respond less well to vaccines than younger adults, and they are more severely affected by infectious diseases, so it is important to understand how age influences lymph node responses.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 19/08/2024, London - Central Research Ethics Committee (3rd Floor, Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 (0) 207 104 8225; londoncentral.rec@hra.nhs.uk), ref: 24/PR/0689

Study design
Non-randomized open-label experimental medicine study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital, Medical and other records

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Human immune responses in lymph node cells after immunisation with a novel Crimean-Congo haemorrhagic fever injection

Interventions
This is an open-label, observational, experimental medicine study investigating human immune responses in lymph node cells after immunisation with a novel Crimean-Congo haemorrhagic fever injection, ChAdOx2 CCHF.

Participants will be healthy adults in two age groups: 18-45 years and ≥65 years. All will have FNA from both armpits, before receiving the study injection and at 7 days after each injection. Participants will be assessed for eligibility at a screening visit; those eligible to take part will attend a further 8 visits, scheduled over 24 weeks. Blood samples will be taken at each visit. Safety will be closely monitored.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
ChAdOx2 CCHF

Primary outcome measure
Frequency, phenotype, and function of immune cells, in axillary secondary lymphoid tissue compared with the blood after intramuscular immunogen challenge with ChAdOx2 CCHF, in older and younger age volunteers measured using multi-parameter analysis of lymph node cells using single cell ribonucleic acid sequencing 5-prime (5' scRNA-seq), and/or multiparameter flow cytometry at baseline/Day 0 and Day 7 after first and second study injections

Secondary outcome measures
Immunogen-reactive lymph nodes measured using ultrasound imaging of secondary lymphoid tissue at baseline/Day 0, Day 7, and Day 28 after the first and second study injections

The following exploratory objectives will be measured at any or all pre and post-injection time points comparing younger with older age groups, before and after injection:

1. Self-reported measures of axillary swelling and tenderness
2. T and B cell responses in axillary secondary lymphoid tissue after intramuscular immunisation
3. Serological responses to CCHF
4. Inflammatory response in the lymph node after immunisation
5. High-resolution tracking of T and B cell clones from LNC (Lymph Node Cells) and PBMC (Peripheral Blood Mononuclear Cells) as they develop after immune challenge

Outcome measures may include but are not limited to the following:
1. Single-cell ribonucleic acid sequencing 5-prime (5' scRNA-seq) to measure cell-by-cell transcriptomes in lymph node cells
2. Cellular indexing of transcriptomes and epitopes sequencing (CITE-seq) to measure cellular antigens on lymph node cells
3. Single-cell T cell receptor sequencing (scTCR-seq) to measure T cell receptor diversity in lymph node cells
4. Immunoglobulin gene sequencing (Ig-seq) to measure B cell receptor and antibody diversity in lymph node cells
5. Phenotypic and functional T cell assays to measure T cell subsets and function, particularly T follicular helper cells using for example an activation-induced marker (AIM) assay, multi-dimensional flow cytometry and ELISpot
6. ELISA to measure binding antibody responses against CCHF

Overall study start date
01/08/2024

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Adults aged between 18 to 45 years (inclusive) OR aged 65 years and over at screening visit.
2. Medically stable (i.e., according to the investigator's 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 the 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, including internet

access for the recording of electronic diary cards.
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, and medical history and have their opinion solicited as to the participant's appropriateness for inclusion.
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): willing to use effective contraception established prior to receiving the first study injection and for the duration of enrolment in the study (and for a minimum of 18 weeks after the final study injection) AND have a negative pregnancy test on the days of screening and study injection.
10. Has previously received any viral vectored vaccine, except for ChAdOx2 CCHF

Participant type(s)
Healthy volunteer

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 16; UK Sample Size: 16

Total final enrolment
18

Key exclusion criteria
1. Participation in another research study involving an investigational product, or which includes procedures that could compromise the integrity of this study (such as significant volumes of blood already taken), within the 12 weeks prior to enrolment, or planned participation in such a study within the study period.
2. Body mass index >=35
3. History of previous confirmed or suspected CCHF infection.
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the study injection.
5. Administration of regular anticoagulation medication likely to induce bruising or bleeding on fine needle aspiration.
6. 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).
7. History of anaphylaxis in relation to vaccination, or local anaesthetic such as lidocaine.

8. History of allergic disease or reactions likely to be exacerbated by any component of the study injection including hypersensitivity to the active substance or to any of the excipients of the study injection or to local anaesthetic such as lidocaine.
9. History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
10. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ) that is not fully resolved.
11. History of any serious psychiatric condition likely to affect participation in the study.
12. For participants of childbearing potential only: participants who are pregnant, breastfeeding or lactating, or are planning pregnancy during the study.
13. 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.
14. History of confirmed major thrombotic event (including cerebral venous sinus thrombosis, deep vein thrombosis, pulmonary embolism); history of antiphospholipid syndrome, or history of heparin induced thrombocytopenia.
15. History of episodes of capillary leak syndrome.
16. 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)
17. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 14 units per week.
18. Suspected or known injecting drug use within the 5 years preceding enrolment.
19. Detectable circulating hepatitis B surface antigen (HBsAg).
20. Seropositive for hepatitis C virus (antibodies to HCV).
21. Seropositive for HIV.
22. 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.
23. 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.

Date of first enrolment
01/10/2024

Date of final enrolment
19/06/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Churchill Hospital
Oxford Vaccine Group

Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Old Road
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OX3 7LE

Study participating centre
John Radcliffe Hospital
Headley Way
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United Kingdom
OX3 9DU

Sponsor information

Organisation
University of Oxford

Sponsor details
Research Governance, Ethics and Assurance (RGEA)
Joint Research Office
1st floor, Boundary Brook House
Churchill Drive
Headington
Oxford
England
United Kingdom
OX3 7GB
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RGEA.Sponsor@admin.ox.ac.uk

Sponsor type
Hospital/treatment centre

Website
https://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

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
Not provided at time of registration

Intention to publish date
31/07/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request directed to Katrina Pollock (katrina.pollock@paediatrics.ox.ac.uk), Chief Investigator or upon written approval of the sponsor.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.0	23/05/2024	09/09/2024	No	No
Protocol file	version 1.1	18/10/2024	26/11/2024	No	No
Protocol file	version 2.0	20/02/2025	08/05/2025	No	No