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# Investigating disruption of the local and systemic human immune response caused by recent Staphylococcus aureus skin infection

**Submission date**
30/07/2024

**Recruitment status**
Recruiting

**Registration date**
21/08/2024

**Overall study status**
Ongoing

**Last Edited**
21/08/2024

**Condition category**
Skin and Connective Tissue Diseases

[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
Staphylococcus aureus is a type of bacteria. It is commonly found living on the skin, particularly in moist areas like the armpits, nose, and groin. It can live in these areas without causing any harm and this is known as colonisation. However, in certain situations it can cause an infection of the skin known as cellulitis, and it can spread into the bloodstream causing more severe and potentially life-threatening disease.
Identifying the active components of an effective immune response to Staphylococcus aureus infection of the skin might help us develop new vaccines to prevent infection or treatments which are more effective than current antibiotics. The aim of this study is to try and understand the differences in the skin and immune system of people who have had recent skin and soft tissue infection caused by Staphylococcus aureus and those who have not.

Who can participate?
Male or female adults from 18 years of age who have had an episode of skin or soft tissue infection in the previous 6 months or healthy volunteer controls

What does the study involve?
This is a non-interventional study collecting samples only. With consent, the researchers will ask participants some questions about their health and perform a brief physical examination. They will then take swab samples from their nose, throat, armpit, and groin and then a blood sample. The researchers will then apply a suction blister device to the forearm which will slowly create three small blisters. These will be the size of 5 pence coins. This suction device may take up to 3 hours to form the blister, during which time participants will have to sit in a chair with an armrest to keep them comfortable. Once the blister is formed, the researchers will take images of it before taking a sample of the blister fluid using a small needle and sterile precautions. Occasionally, they may also take the roof of the blister, however this is no more uncomfortable and will take a similar period of time to resolve. The researchers will give participants a questionnaire to fill in at the end of the visit to get feedback on their experience.
After this visit participants will also be asked to collect their own nose, armpit and groin samples on two more occasions: 1 week later and again 2 weeks after the initial visit. For convenience,

these can be collected in their own home and then either posted back to the researchers with pre-paid envelopes or dropped off at the University of Sheffield Medical School reception. Participants will be provided with training on how to collect and package these samples.
Participants will be invited back to the Royal Hallamshire Hospital for a second visit 21 days after their initial visit. The researchers will check they are happy to continue to participate in the study before repeating some of the procedures done at visit 1. This includes taking swabs from their nose, throat, armpit and groin, blood samples, and producing a suction blister with imaging and sampling of the blister fluid. The researchers will also apply a small microneedle patch to their arm (separately to the site of the suction blister) for 5 minutes before they take images of this area to examine skin healing.
Participants will be asked to complete a daily electronic questionnaire daily for 2 weeks after the initial visit and for 1 week after the second visit. This will be completed on an app on the phone. Any responses will only be accessible to staff working on the study. Participants will also be asked to send pictures of the blisters to the study team via email on a daily basis until they are healed. Participants will be shown how to do this at visit one and be given a device to help them take the images.
A final follow-up questionnaire will be sent to complete electronically 35 days after the initial visit.

What are the possible benefits and risks of participating?
There are no direct benefits to participants. The researchers anticipate a few potential risks of participating, but these may include discomfort and bruising from having blood draws performed, and redness itching or bruising from having negative pressure suction blisters raised on the forearm.

Where is the study run from?
Sheffield Teaching Hospitals NHS Foundation Trust (UK)

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

Who is funding the study?
UK Research and Innovation

Who is the main contact?
Dr Tom Darton, tom.darton@nhs.net

# Contact information

### Type(s)
Scientific, Principal Investigator


### Contact name
Dr Tom Darton

### ORCID ID
http://orcid.org/0000-0003-2209-9956

### Contact details
Department of Infection and Tropical Medicine
Royal Hallamshire Hospital

Sheffield Teaching Hospitals NHS Foundation Trust
Glossop Road
Sheffield
United Kingdom
S10 2JF
+44 (0)114 215 9507
tom.darton@nhs.net

### Type(s)
Public

### Contact name
Mrs Laura Makey

### Contact details
Department of Infection and Tropical Medicine
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Glossop Road
Sheffield
United Kingdom
S10 2JF
+44 (0)114 271 2572
sth.cdsmresearch@nhs.net

## Additional identifiers

### EudraCT/CTIS number
Nil known

### IRAS number

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
STH23188

## Study information

### Scientific Title
Investigating disruption of the local and systemic human immune response caused by recent Staphylococcus aureus skin infection

### Acronym
DEFEND

### Study objectives

What are the hallmark features of disruption to the local and systemic immune response, skin architecture and local microenvironment following recent skin and soft tissue infection caused by Staphylococcus aureus?

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Not yet submitted

## Study design
Single-centre cross-sectional cohort study

## Primary study design
Observational

## Secondary study design
Cross sectional study

## Study setting(s)
Hospital

## Study type(s)
Other

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

## Health condition(s) or problem(s) studied
Cellulitis

## Interventions
In total, up to 40 participants will be recruited (20 to the recent SSTI cohort and 20 to the healthy participant cohort). After the provision of written informed consent and completion of screening procedures, each participant will be seen at two in-person visits. At these visits, they will undergo two negative pressure suction blister (NPSB) procedures with fluid aspiration, one microneedle assessment procedure (using a microneedle array to assess microscopic skin healing function), and skin imaging using optical coherence tomography (OCT). Participants will also be assessed for S. aureus carriage by collection of nasal, groin, and axillary swabs on four occasions (at each visit and twice by self-collected swabs between each visit). Research participant experience surveys will be used to assess the tolerability of study procedures and gather information on overall research subject satisfaction. Blister aspirate and peripheral blood samples will be assessed for immune cell populations by flow cytometry and single-cell sequencing methods.

## Intervention Type
Other

## Primary outcome measure

Combined abundance of immune cell populations in NPSB fluid collected at 2 visits 3 weeks apart (V1/V4), measured by single-cell RNA sequencing (scRNA-seq) within 6 months of an SSTI episode

### Secondary outcome measures
1. Abundance of immune cell populations in peripheral blood (PBMC) collected at baseline (V1) measured using flow-cytometry within 6 months of an SSTI episode
2. Measurement of IgG antibodies to S. aureus antigens (hlA, clfA, SpA, capsular polysaccharide 5 /8) in peripheral blood collected at baseline (V1) measured by multiplex bead array within 6 months of an SSTI episode
3. Combined abundance of immune cell populations in NPSB fluid collected at 2 visits 3 weeks apart (V1/V4) stratified by S. aureus carriage status and measured by scRNA-seq within 6 months of an SSTI episode
4. Skin surface texture, epidermal thickness, depth/morphology of the superficial vascular plexus, optical attenuation measured using OCT imaging at baseline (V1)
5. Microneedle disruption including tissue fluid volume and hole closure kinetics measured at visit 4 using OCT images collected 10, 30 and 60 minutes following microneedle application
6. Subjective participant pain and healing response to study procedures performed at two visits 3 weeks apart (V1/V4) measured using Visual Analog Scale (VAS) and Patient and Observer Scar Assessment Scale (POSAS), respectively
7. Diversity and abundance of skin bacterial populations collected by skin swab at baseline (V1) measured using 16s rRNA sequencing analysis or hs-PCR measurements within 6 months of an SSTI episode

### Overall study start date
01/07/2024

### Completion date
30/09/2026

## Eligibility

### Key inclusion criteria
All participants:
Participants are eligible to be included in the study only if all of the following criteria apply:
1. Adults aged ≥18 years at time of consent
2. Willing and able to provide written informed consent and to comply with the study requirements, according to the investigator’s opinion
3. Agree to provide their National Insurance/Passport number for the purposes of payment of reimbursement expenses
4. Have internet access to allow completion of the e-Diary
5. Be in good general health as determined by medical history, history-directed physical examination, screening investigations performed, and the clinical judgement of the study team

SSTI cohort:
In addition, for the recent SSTI cohort:
1. Have had a recent SSTI probably (i.e. no alternative microbiological diagnosis with a compatible clinical syndrome) or definitely (i.e. confirmed by microbiological laboratory testing) caused by S. aureus infection diagnosed within the 6 months preceding the screening visit

appointment
2. Agree to allow study staff to access their NHS health records (including hospital notes and laboratory records) as required for study purposes

## Participant type(s)
Healthy volunteer, Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
40

## Key exclusion criteria
Participants are excluded from the study if any of the following criteria apply:
1. History or evidence of:
1.1. Chronic dermatological conditions, including eczema, psoriasis, folliculitis, vitiligo, tinea corporis, and atopic dermatitis
1.2. Abnormal or impaired immune function, including congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including oral/inhaled corticosteroids, chemo-/radiotherapy, or monoclonal antibody treatment
1.3. Peripheral vascular (arterial and/or venous) disease
1.4. Clinically significant bleeding disorder, including clotting factor deficiency, coagulopathy, platelet disorder, or current anaemia
1.5. Active cancer/malignancy
2. Active skin or soft tissue infection
3. A history of keloid scarring
4. Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with the evaluation of the study intervention or interpretation of participant safety or study results
5. Inability to comply with any of the study requirements (at the discretion of study staff)
6. Significant blood donation or recent blood (/blood product) donation to NHS Blood and Transplant Service (within 90 days)
7. Tattoos or scarring to the forearm where OCT imaging/NPSB/microneedle assessment procedures will be performed
8. Volunteer incapable of giving fully informed consent

Temporary Exclusion:
Participants will be temporarily excluded from study procedures at V1 and V2 if presenting with the following:
1. Significant acute or acute-on-chronic infection within the previous 7 days or have experienced fever (>37.5°C) or subjective febrile symptoms within the previous 3 days (even with a negative COVID-19 test)
2. History of any antibiotic therapy during the previous 5 days
3. Any systemic corticosteroid (or equivalent) treatment in the previous 14 days, or for more

than seven consecutive days within the past 3 months
4. Anaemia felt to be clinically significant by the study team
5. Receipt of any vaccine including SARS-CoV2 vaccines in the 28 days before or during the study period (D1-D28)
6. Participants meeting any of the temporary exclusion criteria on the day of the challenge will be deferred to a later date for a rescreening appointment, as agreed by the study team and Principal Investigator

### Date of first enrolment
01/10/2024

### Date of final enrolment
01/09/2025

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
**Royal Hallamshire Hospital**
Glossop Road
Sheffield
United Kingdom
S10 2JF

## Sponsor information

### Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

### Sponsor details
Clinical Research and Innovation Office
Glossop Road
Sheffield
England
United Kingdom
S10 2JF
+44 (0)114 271 2572
sth.researchadministration@nhs.net

### Sponsor type
Hospital/treatment centre

**Website**
https://www.sheffieldclinicalresearch.org/

**ROR**
https://ror.org/018hjpz25

# 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

# Results and Publications

**Publication and dissemination plan**
The results of the study will be presented at local, national and international conferences and meetings, published in pre-print or peer-reviewed scientific journals, as appropriate. Participant anonymity will be maintained in any published material. The data collected may be used to contribute to educational projects including postgraduate research degrees.

**Intention to publish date**
30/09/2027

**Individual participant data (IPD) sharing plan**
The datasets generated during the current study will be stored in a publicly available repository (ORDA, https://orda.shef.ac.uk/). Data stored will include anonymised clinical metadata, the microbiological, immunology and genetic data, including host transcriptomics and protein interaction analysis. All decisions regarding data sharing with new users during the active study will be made by the study principal investigator after consultation with the Steering Committee, the study Data and Safety Management Committee and the University of Sheffield Research Data Management team. Reasonable requests will not be refused, although a formal data-

sharing agreement may be required in certain cases. Data (and related code/software) will be made available publicly immediately at the time of result publication. User responsibility with the data will be governed by the relevant Creative Commons license.

### IPD sharing plan summary

Stored in publicly available repository, Available on request