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Vaccination for immune recovery following sepsis

Submission date	Recruitment status	[_] Prospectively registered
20/11/2018	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/12/2018	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
12/08/2025	Infections and Infestations	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Many patients who survive an Intensive Care Unit (ICU) admission with sepsis are at much higher risk of getting new infections after they leave hospital; the exact reasons are unclear. These repeated incidents of infections often result in weakening the patients' health. It was recently found that a specific subgroup of white blood cells that are responsible for the protection against common bacteria are reduced in sepsis survivors. This defect is likely to weaken the body's defenses and thus increase the risk of re-infection in sepsis survivors. This study is being conducted to find out if a safe vaccine will help the damaged immune system of sepsis survivors to recover and prevent these infections. Participants of this study will be followed up for one year after their first admission with sepsis to determine whether vaccination reduces infection rate and severity during this time. Blood samples are also taken to determine the ways by which vaccination might work.

Who can participate?
Sepsis patients aged 18 years or older who are well enough to leave the ICU

What does the study involve?
Patients are randomly allocated into one of two groups. One group receives a single injection of vaccine. The other group receives a dummy vaccine that contains no active ingredients. Blood samples (equivalent to 2.5 tablespoons = 40 ml) are taken before the injection and 10 days later if they are still in hospital. Women with child-bearing potential take a pregnancy test before getting the injection. Participants keep a vaccine diary for 7-10 days to record any pain, fever, swelling or other symptoms at the point where the injection was given. Their medical notes are reviewed to find out if the treatment has had any effect. As part of the follow-up, participants visit the outpatient clinic for further tests at 30 days and 90 days of starting the trial. Blood samples are taken using a small needle to keep the pain or discomfort to a minimum. During these visits, participants are asked about their health using questionnaires, any recent change in medications or new medications are recorded, and a blood sample is taken. Participants are contacted over the phone at 6 and 12 months with a questionnaire about general health and to measure any residual effects of their illness. These take about 15 minutes to complete.

What are the possible benefits and risks of participating?
It is hoped that the treatment will reduce the number and severity of new infections, but his may not happen. There will be no direct benefit from taking part in this study but the information gained from participation may help to improve treatment of sepsis survivors in the future. The further benefit to patients is that additional the follow-up visits to check their health at 30 days and 90 days following discharge from hospital. Known side effects of the vaccine are:
Very common (≥ 1 in 10): headaches, chills, fatigue, vaccination site erythema/pain/swelling, limitation of arm movement, joint pain, muscle pain, decreased appetite, diarrhoea, vomiting, rash.
Common (≥ 1/100 to < 1/10): fever (very common in adults aged 18 to 29)
Uncommon (≥ 1/1,000 to < 1/100): nausea, lymphadenopathy (swollen lymph nodes), hypersensitivity reaction

Where is the study run from?
St Thomas' Hospital (UK)

When is the study starting and how long is it expected to run for?
June 2017 to July 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof Manu Shankar-Hari, manu.shankar-hari@ed.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-002236-17

ClinicalTrials.gov (NCT)
NCT03565159

Protocol serial number
36862

Study information

Scientific Title
VACIRISS: pneumococcal Vaccination to ACcelerate Immune Recovery In Sepsis Survivors: a randomized placebo-controlled trial

Acronym
VACIRISS

Study objectives
The aim of VACIRiSS trial is to evaluate the immunogenicity and heterologous effects of single dose 13-valent conjugate pneumococcal vaccine (PCV-13) in preventing infection related rehospitalisation or death in sepsis survivors and to collect outcome event data with necessary precision to inform future definitive trial design.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East Midlands - Leicester Central Research Ethics Committee, 16/04/2018, ref: 230431

Study design
Randomised; Interventional; Design type: Prevention, Drug, Vaccine

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Infection following recovery from sepsis

Interventions
The aim of VACIRiSS trial is to evaluate the immunogenicity and heterologous effects of single dose 13-valent conjugate pneumococcal vaccine (PCV-13) in preventing infection related rehospitalisation in sepsis survivors and to collect outcome event data with necessary precision to inform future definitive trial design.

Study design and rationale:
The VACIRiSS trial is a phase IV, multi-centre placebo-controlled randomised trial of conjugate pneumococcal vaccine in adult sepsis survivors with an internal pilot phase.
The internal pilot phase will run until 25% of sample size (n=54 patients) are recruited and the last recruited patient has had a 6-month follow-up. The internal pilot phase generates feasibility data and will include a focus group discussion. The trial recruitment will continue whilst the analysis of internal pilot phase is being completed.
The trialists chose a placebo-controlled RCT design to obtain an unbiased estimate of the causal effect of the intervention on the outcome. Randomisation also ensures that measurable and, more importantly, unmeasurable characteristics are distributed in a way that reduces confounding to chance. Random allocation of subjects and allocation concealment will ensure that investigator bias is not an issue. There is limited information of how sepsis survivors patients might respond to vaccination and as such this trial will provide that information, in an unbiased manner. Currently, there is no proof that vaccination will benefit these patients and there is clinical equipoise for this trial.

The broad timetable for the stages of the research:
The trial will be conducted in six National Health Service Adult General intensive care units or high dependency units in the United Kingdom. The trial aims to start recruiting patients February 2018. The patients enrolled in the trial will be followed up for a total of 365-days. The trialists anticipate the final patient will be recruited into the trial by January 2021. They plan to conduct a focus groups discussion at the end of the internal pilot phase. As part of the trial, blood samples will be collected for studying exploratory outcomes.

Will there be planned interim analyses/reports?
The trialists plan to do a single interim analysis, to correspond with the internal pilot phase of the trial using Peto-Haybittle stopping rule ($p<0.001$) to recommend early termination of the trial due to either effectiveness in reducing proportion of reinfections by 30 days or harm. They will also do further interim analyses if requested by the Data Monitoring and Ethics Committee (DMEC).

The sampling and sample sizes for the project
The trial will recruit 214 patients in total. The target population are adult patients who survive to hospital discharge following an index intensive care units or high dependency units admission episode of sepsis or septic shock. There are no previous randomised controlled trials in this population from which to estimate the magnitude of the treatment effect of conjugate pneumococcal vaccination to reduce reinfection risk. Extrapolating from the two systematic reviews we completed, the trialists estimate that by 1 year, 60% of sepsis survivors are re-hospitalised with 66% of rehospitalisations' being infection-related and 16% die over the same time. Thus, the overall rate of infection-related hospitalisation or death was estimated as 55.6%.

A sample size of 214 adults will be sufficient to give 90% power to detect a hazard ratio of 0.5 (P<0.05) using time-to-event analysis.

How participants will be identified, approached and sampled?
Potentially eligible participants will be approached about the study (i.e. all sepsis patients aged 18 or older). Lab results within 72 hours of screening are valid for assessing potential eligibility criteria for the trial. Patients who meet all the following inclusion criteria and none of the exclusion criteria are potentially eligible to participate in the trial. Full eligibility will be assessed after obtaining written informed consent.
All intensive care units or high dependency units admissions with sepsis are potentially eligible for this trial. Potentially eligible patients will be identified by the local research team as per local arrangements.
This identification process should start as patients are recovering from the critical illness. The term recovering is defined as subjective clinical improvement with reducing organ support requirements such that they are expected to be discharged from the critical care unit in the next 2-5 days.
Participants will be recruited from adult intensive care units and high dependency units in NHS hospitals. Patients will be consented by investigators included in the delegation log. Consent and screening should be completed prior to step down from intensive care units / high dependency units and within 5-days of assessment if potentially eligible. Following consent full eligibility review will be undertaken. Screening log will record the reasons for not enrolling patients who have consented.
As patients are recovering from critical illness, they may be unable to give informed consent due to the residual effects of sedation, ongoing delirium and impaired cognition. In this context, consent/advice will therefore be obtained from the legal representative in line with the legal requirements for obtaining advice in patients without capacity in England, Wales and Northern Ireland (Mental Capacity Act 2005), and consent in Scotland (Adults With Incapacity (Scotland) Act 2000). Consent process will be completed with the patients, as soon as they regain capacity. Patients without a legal representative will not be eligible to participate in this trial.

Participants are randomised to receive either the pneumococcal vaccine or a placebo injection. Blood samples (equivalent to 2.5 tablespoons = 40ml) are taken before the injection and at 10 days following the injection if they are still in hospital.Females with child-bearing potential take a pregnancy test before getting the injection. Participants will be asked to keep a vaccine diary for 7-10 days, to record any pain, fever, swelling or other symptoms at the point where the injection was given. Their medical notes will be reviewed by the doctors and nurses from your hospital to find out if the treatment has had any effect. The doctors and nurses from your hospital will visit prior to leaving hospital to collect the vaccine diary and to take blood samples. As part of the follow-up, participants will need to visit the outpatient clinic for further tests at 30 days and 90 days of starting the trial. They will be given appointment letters to attend the follow-up clinic for these visits. These samples will be taken using a small needle to keep the pain or discomfort to a minimum. During these visits, they will be asked about their health using questionnaires, any recent change in medications or new medication and a blood sample will be taken. The research team will then contact them over the phone at 6 and 12 months with a questionnaire about general health and will measure any residual effects of illness. These will take about 15 minutes to complete.

Intervention Type
Biological/Vaccine

Phase

Phase IV

Drug/device/biological/vaccine name(s)
PCV-13

Primary outcome(s)
Time to first infection-related rehospitalisation or death, measured using patient follow-up within the 365-day follow-up period (no specific timepoints)

Key secondary outcome(s))
Secondary outcome measures:
Rehospitalisation, reinfections, reinfection-related rehospitalisation, and time to first antibiotic therapy in general practice, measured using patient follow up at different follow-up time points within the 365 days follow-up period

Tertiary outcome measures:
Feasibility of the initial qualitative thematic analysis of internal pilot phase.

Exploratory outcome measures of immune recovery patterns:
1. Anti-pneumococcal antibody, measured using ELISA at baseline and 30 (+/-7) days
2. Immune recovery patterns and heterologous vaccine effects, measured using flow cytometry at baseline (T0) before IMP administration, on 10 (+/-3) days post T0 in patients still in hospital, on 30 (+/-7) days' post T0 and 90(+/-7) days post T0

Completion date
31/07/2023

Eligibility

Key inclusion criteria
1. Aged 18 years or older at screening
2. Registered with a General Practitioner
3. Admitted to intensive care unit or high dependence unit for sepsis (sepsis is defined as suspected or proven infection with a total Sepsis-related Organ Failure Assessment (SOFA) score of at least 2 points)
4. Improved clinical condition
5. Ready for step down to high dependence unit or ward-based care in the next 24-48 hours
6. Patient or their legal representative is able to provide written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
214

Key exclusion criteria
1. Core temperature 38.0 °C or higher within the past 24 hours prior to study investigational medicinal product (IMP) administration
2. Hypersensitivity reaction (i.e. anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine
3. Vaccination administered to patient within 7 days of enrolment
4. Pregnant or lactating women
5. Limitations of care set, including not for resuscitation, not for readmission to critical care
6. Resident of nursing home, long-term care facility or other institution, or requirement of semi-skilling nursing care
7. Coagulopathy, defined as at least one of the following:
7.1. Platelet count less than 50 x 109/L
7.2. International normalized ratio (INR) greater than 1.3
8. APACHE II score-defined immune deficiency or supression, defined as at least one of the following conditions:
8.1. Documented human immunodeficiency virus (HIV) infection at any timepoint prior to the trial (if previous results are not available and/or current admission is not due to HIV infection, these patients do not need new testing and are considered eligible for the trial)
8.2. Leukaemia, defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
8.3. Lymphoma, defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
8.4. Hodgkin disease, defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
8.5. Multiple myeloma, defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
8.6. Malignancy, defined as presence of any malignancy that had been treated by or had been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
8.7. Chronic renal failure (defined as receipt of renal dialysis or transplant) or nephrotic syndrome
8.8. Receipt of immunosuppressive therapy, including steroids, within 3 months of study vaccine administration (For corticosteroids, prednisone or equivalent 0.5 mg/kg/day for 14 days or longer. Inhaled, intra- articular, and topical steroids are not considered immunosuppressive)

Date of first enrolment
01/08/2018

Date of final enrolment
20/04/2022

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
St Thomas' Hospital (lead site)
ICU Offices
London
United Kingdom
SE1 7EH

Study participating centre
King's College Hospital
Anaesthetics Critical Care Emergency and Trauma
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
University College London Hospital
Critical Care Unit
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Addenbrooke's Hospital
John Farman Intensive Care Unit
D3 Mail Box 17
Hills Road
Cambridge
United Kingdom
CB2 2QQ

Study participating centre

Royal Victoria Hospital
Regional Intensive Care Unit
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
Royal Infirmary of Edinburgh
GU309
Chancellors Building
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB

Study participating centre
Royal Gwent Hospital
Aneurin Bevan University Health Board
c/o 13 Clytha Square
Cardiff Road
Newport
United Kingdom
NP20 2EF

Study participating centre
John Radcliffe Hospital
Oxford University Hospitals NHS Foundation Trust
Headley Way
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United Kingdom
OX3 9DU

Study participating centre
Royal Surrey County Hospital NHS Foundation Trust
Egerton Road
Guildford
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GU2 7XX

Study participating centre
Musgrove Park Hospital
Taunton and Somerset NHS Foundation Trust
Taunton
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TA1 5DA

Study participating centre
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Cosham
United Kingdom
PO6 3LY

Study participating centre
Wythenshawe Hospital
Manchester University NHS Foundation Trust
Southmoor Road
Manchester
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M23 9QZ

Study participating centre
Manchester Royal Infirmary
Manchester University NHS Foundation Trust
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Manchester
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M13 9WL

Study participating centre
Sunderland Royal Hospital
South Tyneside and Sunderland NHS Foundation Trust
Sunderland
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SR4 7TP

Sponsor information

Organisation
Guy's and St Thomas' NHS Foundation Trust

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Government

Funder Name
NIHR Trainees Co-ordinating Centre (TCC); Grant Codes: NIHR-CS-2016-16-011

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	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes