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Clinical characterisation protocol for severe emerging infection

Submission date	Recruitment status
27/03/2020	No longer recruiting
Registration date	**Overall study status**
21/04/2020	Ongoing
Last Edited	**Condition category**
16/04/2024	Infections and Infestations

✓ Retrospectively registered
✓ Protocol added
? SAP not yet added
✓ Results added
? Raw data not yet added
✓ Record updated in last year

Plain English Summary
Background and study aims
Infectious disease is the single biggest cause of death worldwide. New infectious agents require investigation to understand its characteristics and how infection with this pathogen results in a disease process. We need to understand risk factors for severe illness and how to best treat disease caused by this pathogen. In order to develop a mechanistic understanding of disease processes, such that risk factors for severe illness can be identified and treatments can be developed, it is necessary to understand pathogen characteristics associated with virulence, the replication dynamics and in-host evolution of the pathogen, the dynamics of the host response, the pharmacology of antimicrobial or host-directed therapies, the transmission dynamics, and factors underlying individual susceptibility.
This study is designed for the rapid, coordinated clinical investigation of patients with confirmed infection with a pathogen of public interest. The study has been designed to maximize the likelihood that as much data as possible is collected and shared rapidly in a format that can be easily aggregated, tabulated and analysed across many different settings globally. The study is designed to have some level of flexibility in order to ensure the broadest acceptance.

Who can participate?
Any patient of any age who is admitted to a participating acute hospital with confirmed infection with a pathogen of public interest.

What does the study involve?
The study can be delivered at different Tiers according to local resources at participating sites. In all instances, data regarding clinical presentation (symptoms and clinical signs), treatments in hospital, past medical history/background for all patients in the study are collected throughout their hospital admission.
For sites operating at Tier 0: there is the above data collection only.
For sites operating at Tier 1: there is the above data collection and samples are taken from patients on the first day in the study (blood samples, throat swab, collecting fluid from the nose and mouth (using safe, specialised equipment), urine, faeces).

For sites operating at Tier 2: the above data collection, and samples as mentioned above on the first day in the study and at subsequent time points in the first two weeks of their hospital admission. Four weeks after discharge, patients are invited back to have repeat samples taken.

What are the possible benefits and risks of participating?
Benefits: There will be no direct benefit to research participants. The study may include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. The results of this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The feasibility of this will depend on local resources. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.
Risks: Inconvenience. Participation in this research study poses a minimal risk of inconvenience through household visits and attendance of follow-up visits. Appropriate compensation for travel costs to attend follow-up visits and for time of attending visits will be given according to the standard policies of the sponsor.
Phlebotomy. Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Daily blood draw volumes have been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.
Discomfort of throat swabs. Collecting throat swabs may be cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff at each site, and samples will be taken at the same time as clinical samples in order to minimize these risks.
Discomfort of SAM strips. Collecting nasal fluid using SAM strips may be cause a transient tickling sensation during application and removal which can cause eye watering through a local reflex.
Oral (Crevicular) Fluid Collection. Oral crevicular fluid collection involves the participant or carer gently brushing a small sponge on a flexible plastic rod at the margin of the gums and teeth in exactly the same manner as is done for routine mouth care or teeth brushing. Apart from inconvenience and sensation, there is no expectation of and discomfort.
Incidental findings in genetic testing. This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant's health. Since the samples will be analysed anonymously in batches, and generally in non-clinical laboratories with investigational techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.
at risk venepuncture will be minimised by limiting research venepuncture to coincide with clinical venepuncture.

Where is the study run from?
The study is run from participating acute hospital sites in England, Wales and Scotland.

When is the study starting and how long is it expected to run for?
February 2020 to July 2027

Who is funding the study?
1. Wellcome Trust (UK)
2. Medical Research Council (UK)

3. SPRINT-SARI NIHR Health Protection Research Unit (HPRU) in Respiratory Infection (UK)
4. HPRU in Emerging and Zoonotic Infections (UK)

Who is the main contact?
Unfortunately, this study is not recruiting public volunteers at this time. This is because the research isn't ready for volunteers yet or the researchers are directly identifying volunteers in certain areas or hospitals. Please do not contact the research team as they will not be able to respond. For more information about COVID-19 research, visit the Be Part of Research homepage.

Study website
https://isaric4c.net

Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
126600

ClinicalTrials.gov number
Nil known

Protocol/serial number
IRAS 126600, CPMS 14152

Study information

Scientific Title
ISARIC WHO Clinical Characterisation Protocol for severe emerging infections UK: ISARIC WHO CCP-UK

Acronym
ISARIC WHO CCP-UK

Study hypothesis
The rapid, coordinated clinical investigation of severe or potentially severe acute infections by pathogens of public health interest

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/02/2020, Oxford C Research Ethics Committee (Formally Oxford South Central C) (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8041; oxfordc.rec@hra.nhs.uk), ref: 13/SC/0149

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
https://isaric4c.net/sample_access

Condition
Emerging infections

Interventions
Patients with confirmed infection with pathogen of public interest, or an appropriate consultee, will be approached by staff who will explain the details of the study to the patient or consultee and allow them time to discuss and ask questions. Patients who agree to be in the study will sign an informed consent form.

Patients will have a daily clinical review as per standard care and the following samples will be obtained:
1. Pathogen samples
- residual volumes of routine clinical samples will be stored
- the following samples will be obtained daily for the first week, every two days for the second week and weekly until resolution of acute disease to a maximum of 100 days:
Respiratory tract samples - samples from the throat (nasopharyngeal aspirates) or if the patient is on a ventilator, a sample from the windpipe (ET aspirate)
Blood
Urine
Stool
Swabs from infected sites (eg. skin lesions)

Pathogen samples will be examined by growing the infectious agent in a laboratory, and by reading its genetic code to understand how it changes over time and develops new characteristics. This will also tell us how the pathogen may be spread and how long people are infectious for.

2. Blood samples
A blood sample will be taken at recruitment, day 3, 9 and 28 days after recovery. The volume of blood depends on the weight of the patient as per the study protocol.

Samples will be tested for a range of measures of immune function, including antibody production and immune signalling molecules. This will enable us to better understand the immune response to infection.

Intervention Type
Other

Primary outcome measure
At baseline, day three, day nine and > 28 days after hospital discharge:
1. Changes in pathogen during infection and during spread between individuals and development of resistance measured using:
1.1. Respiratory samples:
1.1.1. Nasal SAM strip
1.1.2. Throat swab in virus transport medium

1.1.3. Endotracheal aspirate if intubated,
1.1.4. Where resources permit, in infants/children who cannot take SAM strip, nasopharyngeal aspirate OR flocked nose swab in virus transport medium
1.2. Urine (up to 10ml)
1.3. Stool (up to 10ml) or rectal swab
1.4. Samples from infected sites/sores
1.5. Any residual from samples taken for clinical care
2. Non-invasive determination of humoral immune response measured using oral fluid (Crevicular fluid)
3. Mediators/biomarkers and serology measured using blood sample in serum (clotted) tube
4. Mediators/ metabolites/ biomarkers and RNA/DNA from pathogens measured using blood sample in EDTA tube
5. Microarray/RNA sequencing pathogen & host transcriptome measured using blood sample in blood RNA tube TempusTM (or PAXgene®)
6. For CNS infections only: additional cerebrospinal fluid sample during clinical lumbar puncture to measure Mediators/ metabolites/ biomarkers and RNA/DNA from pathogens and to perform serological testing for pathogen-specific antibodies

Secondary outcome measures
None

Overall study start date
12/03/2013

Overall study end date
28/07/2027

Eligibility

Participant inclusion criteria
1. Patients (children and adults) with confirmed infection with a pathogen relevant to the study objectives
2. Inclusion criteria for SARI patients:
2.1. Acute respiratory illness patients of all ages with a history of fever or measured fever of >38° C and at least one respiratory symptom
2.2. High suspicion or confirmed infection with a respiratory pathogen relevant to the objectives of this protocol
2.3. Admitted to a healthcare facility
3. Inclusion criteria for VHF patients:
3.1. Sudden onset high fever and known contact with a person with suspected or confirmed VHF
3.2. Sudden onset of fever with at least three of the following symptoms: headache; anorexia; lethargy; aching muscles or joints; breathing difficulties; vomiting; diarrhoea; stomach pain; dysphagia; hiccups
3.3. High suspicion or confirmed infection with a VHF pathogen relevant to the objectives of this protocol
3.4. Admitted to a healthcare facility
4. Inclusion criteria for patients with CNS infection
4.1. Fever >=38C or history of fever within 30 days in patients of all ages with one of:
4.1.1. Altered consciousness (including reduced conscious level, confusion, or a change in personality or behaviour)
4.1.2. New onset of seizures (excluding simple febrile seizures)

4.1.3. New onset focal neurological deficit
4.2. Electroencephalographic (EEG), neuroimaging or cerebrospinal fluid examination findings indicative of central nervous system infection
4.3. High likelihood of infection with a neuroinvasive pathogen of public health interest
4.4. Admitted to a healthcare facility
OR
4.5. Confirmed infection with a neuroinvasive pathogen of public health interest and admitted to a healthcare facility
5. Inclusion criteria for patients with infection by pathogens of public health interest:
This study will enrol eligible patients with suspected or confirmed infection with a pathogen of public health interest. These pathogens will be listed by the investigators taking into consideration position statements issued by World Health Organisation, Public Health England and other authorities.

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
Planned Sample Size: 100; UK Sample Size: 100

Participant exclusion criteria
Refusal to participate

Recruitment start date
06/02/2020

Recruitment end date
28/02/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Wythenshawe Hospital
Manchester University NHS Foundation Trust
Southmoore Road
Wythenshawe

Manchester
United Kingdom
M23 9QT

Study participating centre
Acute NHS trusts and Community Hospital NHS Trusts and Mental Health NHS Trusts in the United Kingdom are open to recruitment
United Kingdom
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Sponsor information

Organisation
University of Oxford

Sponsor details
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Sponsor type
University/education

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

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
SPRINT-SARI NIHR Health Protection Research Unit (HPRU) in Respiratory Infection

Funder Name
HPRU in Emerging and Zoonotic Infections

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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?
Protocol file	version v8.2	17/02/2020	21/04/2020	No	No
Protocol article	protocol and results	22/05/2020	28/05/2020	Yes	No
Results article	results for children and young people	27/08/2020	28/08/2020	Yes	No
Results article	results	09/09/2020	11/09/2020	Yes	No
Results article	in-hospital mortality results	01/07/2021	18/05/2021	Yes	No
Results article	hospital bed pathway results	09/06/2021	11/06/2021	Yes	No
Results article	Implementation of corticosteroids	28/03/2022	28/03/2022	Yes	No
Results article	Outcome of COVID-19 in hospitalised immunocompromised patients	31/01/2023	02/02/2023	Yes	No
HRA research summary			28/06/2023	No	No
Results article	in-hospital mortality in patients with and without cancer	12/04/2024	16/04/2024	Yes	No