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Community-acquired sepsis-like syndrome and paediatric acute respiratory tract infection in childhood study

Submission date
10/08/2016

Recruitment status
No longer recruiting

Registration date
30/08/2016

Overall study status
Completed

Last Edited
30/08/2016

Condition category
Infections and Infestations

- [ ] Prospectively registered
- [ ] Protocol
- [ ] Statistical analysis plan
- [ ] Results
- [ ] Individual participant data
- [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Sepsis-like syndrome (SLS, or blood infection) and acute respiratory infection (ARI, or chest infection) are two of the main types of severe viral infection in children. Often these children are so unwell they have to go to hospital. Rarely, long-term problems and even death can result from the infection. In the past bacteria were the main causes for many severe infections. However, due to successful vaccine programmes, viruses are now mostly to blame. This is worrying as viruses have the potential to cause large-scale outbreaks affecting the health of many people, as was the case in the recent worldwide swine flu outbreak. The focus of this study will be the specific viruses that are known to play a role in a proportion of severe cases of SLS and ARI. A better understanding of the role of viruses will help us to diagnose and manage affected children and work out how to better respond to outbreaks. The aim of this study is to look at the causes, symptoms, clinical management, impact and outcomes for children with SLS and ARI. In addition, many viruses traditionally thought to be important causes of SLS and ARI are being detected in children without symptoms. This will be considered by also inviting children without symptoms of SLS or ARI to participate in the study.

Who can participate?
1. Hospitalised infants (under 6 months old) with signs of blood infections
2. Hospitalised children (under 6 years old) with signs of chest infections
3. Children with no signs of severe infection, attending hospital for surgery, x-ray, blood test etc

What does the study involve?
Samples are collected from all participants on their day of admission to hospital, including nose swabs, urine, blood and stool samples, as well as cerebrospinal fluid (a body fluid found in the brain and spine), if taken as part of routine treatment, along with other information from the child's medical notes. For the children with signs of blood/chest infections, clinical observations, medications and clinical management are recorded on admission and weekly until discharge or day 30 of hospitalisation (whichever comes first). A few of the children with blood infections are also followed up one year later.

What are the possible benefits and risks of participating?
There are no direct benefits to either the child or the legal guardians/carers of the child, for participating in this study. However, many people find it a real benefit to help in a study which may change how we care for children in the future. There are very few risks associated with this study, as we do not intend to collect any additional samples from the child. On the rare occasion that additional blood samples are needed, the skilled teams will do everything they can to reduce any discomfort to the child, such as using a cream which helps to numb the skin.

Where is the study run from?
1. St George's University of London (UK)
2. University of Tartu (Estonia)
3. C.H. Regionaire Universitaire de Lille (France)
4. H. U. Robert Debrè. Paris (France)
5. National and Kapodistrian University of Athens (Greece)
6. Aristotle University Thessaloniki (Greece)
7. Universittasklinikum Freiburg (Germany)
8. Azienda Ospedaliera di Padova (Italy)
9. Ospedale Pediatrico Bambino Gesù (Italy)
10. Vilnius University Children's Hospital (Lithuania)
11. Victor Babes Clinical Hospital (Romania)
12. Hospital 12 de Octubre (Spain)
13. Hospital Clinico de Santiago de Compostela (Spain)
14. Kinderspital Zurich (Switzerland)
15. Alder Hey Children's NHS Foundation Trust (UK)
16. Great Ormond Street Hospital (UK)

When is the study starting and how long is it expected to run for?
August 2015 to December 2018

Who is funding the study?
Seventh Framework Programme (Belgium)

Who is the main contact?
Dr Jessica Jarvis

Contact information

Type(s)
Scientific

Contact name
Dr Jessica Jarvis

Contact details
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Protocol version 1.0 (18/09/2015)

Study information

Scientific Title
Multi-centre EuRopean study of MAjor Infectious Disease Syndromes (MERMAIDS): community-acquired sepsis-like syndrome and paediatric acute respiratory tract infection in childhood

Acronym
PED-MERMAIDS

Study objectives
Sepsis-like syndrome (SLS) and acute respiratory tract infection (ARI) are frequent causes of hospitalisation in infants and young children, and pose a risk of severe outcomes and potentially also of long-term complications. Both can be caused by pathogens with epidemic potential, importantly enterovirus (EV) and human parechovirus (HPeV) for SLS, and respiratory syncytial virus (RSV), FLU, human rhinovirus (HRV), S. pneumoniae for ARI. A better understanding of the role of these pathogens can inform diagnostics, surveillance and management in this vulnerable age group as well as prevention and outbreak response management.

The overall aim of this observational, case-control study is to prospectively study the aetiology, diagnostics, clinical management, impact and outcomes across Europe of:
1. Community-acquired sepsis-like syndrome in hospitalised infants (<6 months old)
2. Community-acquired acute respiratory tract infection in hospitalised children (<6 years old)

The study will focus on specific pathogens known to be aetiological agents of the two syndromes of interest (SLS and ARI). The study will also contribute to capacity building within the paediatric PREPARE network aimed at establishing early and robust European responses to (re-)emerging infections including rapid identification, control and research responses.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - City & East Research Ethics Committee, 02/03/2016, REC ref: 16/LO/0163

Study design
Observational prospective case-control study

Primary study design
Observational

Secondary study design
Case-control 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
Sepsis-like syndrome (SLS) and acute respiratory infections (ARI) in children

Interventions
ELIGIBILITY
Participants will be assessed against pre-determined eligibility criteria (inclusion and exclusion criteria). Cases will be assessed at the time of presentation or within 24 hours of admission.

This study will recruit children into three groups:
1. Infants (<6 months old) admitted to a participating hospital with a new episode of community-acquired sepsis-like syndrome
2. Children (< 6 years old) admitted to a participating hospital with a new episode of community-acquired acute
respiratory infection
3. Age-matched afebrile controls (< 6 years old)

STUDY PROCEDURES FOR PARTICIPANTS WITH SLS OR ARI

Informed consent (Day 0) with the option of deferred consent will be sought. All participants for whom legal guardians/carers have provided informed consent will have a baseline assessment that will be recorded on a designated CRF. This will include:
1. Demographics, medical history, physical examination findings and vital signs
2. Basic information on clinical management
3. Results of routine investigations

Sampling (Day 0-1)
For SLS and ARI cases, research-specific samples (blood, urine, nasopharyngeal, stool, and if available CSF) will be obtained with the first set of routine samples within 24 hours of admission (day 0) and processed once eligibility has been confirmed and written informed consent has been obtained.

Clinical data
Clinical observations, medications and clinical management will be recorded in the CRF on admission/baseline
assessment (Day 0), and weekly (every 7 days) for cases until discharge, death or day 30 of hospitalisation (whichever comes first)

Weekly clinical data will include:
1. Documentation of survival status, total days of supplemental oxygen, total days of invasive or non-invasive ventilator support and total days of pharmacological inotropic support
2. Admission to Paediatric Intensive Care Unit or Paediatric High Dependency Unit, and total length of stay, receipt of immunomodulators and duration of antibiotic and/or antiviral exposure during hospitalisation
3. Neurological complications (SLS cases)
4. Developmental assessment at 12 months of age (subgroup SLS cases)

Follow up visits
Follow-up visits are not planned for most cases or controls, except for a subgroup of approximately 40 SLS cases. They will be invited for developmental assessments at 12 months of age.

STUDY PROCEDURES FOR CONTROLS

Informed consent (Day 0)
For controls, deferred consent will not apply as their admission will be planned and not an emergency. Research-
specific samples will be obtained only after parental informed consent has been given.

Baseline assessment (Day 0)
All participants for whom legal guardians/carers have provided informed consent will have a baseline assessment
that will be recorded on a designated CRF. This will include:
1. Demographics
2. Medical history
3. Physical examination findings
4. Vital signs

Sampling (Day 0-1)
Samples will include nasopharyngeal swab, blood, urine and stool samples
Follow-up visits are not planned for controls

Intervention Type
Other

Primary outcome measure
SLS
1. The proportions of infants with SLS in whom EV or HPeV is detected in blood (day 0) and the strength of association between EV or HPeV detection in blood in SLS cases compared to controls (odds ratio and 95% CI)
2. The proportions of infants with SLS in whom EV or HPeV is detected in nasopharyngeal and/or stool samples (day 0) and the strength of association between EV or HPeV detection in nasopharyngeal and/or stool samples in SLS cases compared to controls (odds ratio and 95% CI)

ARI
The proportions of infants with ARI in whom RSV, FLU, HRV or S. pneumoniae is detected in nasopharyngeal samples (day 0) and the strength of association between their detection in nasopharyngeal samples in ARI cases compared to controls (odds ratio and 95% CI)

Secondary outcome measures

SLS
1. Association between viral load in blood on day 0 and disease severity
2. Association between pathogen co-detection on day 0 and disease severity
3. Subtypes of EV or HPeV identified in blood collected on day 0
4. Characterisation of key parameters describing clinical management of SLS including:
4.1. Proportion admitted to intensive care (and duration) during hospitalisation
4.2. Proportion treated with antimicrobials, antivirals and/or immunomodulators during admission (and average duration of treatment)
4.3. Proportion of cases requiring during admission: supplemental oxygen, non-invasive or invasive mechanical ventilation, extra-corporeal life support
4.4. Duration of invasive mechanical ventilation and extra-corporeal life support, if applicable
4.5. Average length of hospitalisation (in days)
4.6. In-hospital mortality
5. Bayley scales of infant development and Denver II developmental screening test at discharge and at 12 months of age in a subset of 40 SLS cases
Severe disease will be defined as cases with requirement for supplementary oxygen, ventilatory and/or inotropic support (pharmacological or mechanical) and/or cases who die in hospital (all-cause mortality)

ARI
1. Association between viral load in nasopharyngeal swabs on day 0 and disease severity
2. Association between bacterial load in nasopharyngeal swabs on day 0 and disease severity
3. Association between pathogen co-detection in nasopharyngeal swabs on day 0 and disease severity
4. Characterisation of key parameters describing clinical management of ARI including:
4.1. Proportion admitted to intensive care during hospitalisation and average length of stay
4.2. Proportion treated with antimicrobials, antivirals and/or immunomodulators during admission (and average duration of treatment)
4.3. Proportion of cases requiring during admission: supplemental oxygen, non-invasive or invasive mechanical ventilation, extra-corporeal life support
4.4. Duration of invasive mechanical ventilation and extra-corporeal life support, if applicable
4.5. Average length of hospitalisation (in days)
4.6. In-hospital mortality
5. Comparison of gene expression profiles (microarray) associated with SARI in adult patients to gene expression profiles in children with severe disease ARI
Severe disease will be defined as cases with requirement for supplemental oxygen and/or ventilatory and/or inotropic support (pharmacological or mechanical) and/or cases who die in hospital (all-cause mortality)

Overall study start date
01/08/2015

Completion date
31/12/2018

Eligibility

Key inclusion criteria
The study will recruit into three groups (SLS, ARI and controls), each with different inclusion criteria.

SLS Group Cases:
1. Age <6 months old on the day of admission (day 0) into the study
2. Onset of symptoms within 7 days
3. The attending physician has decided that the infant requires hospitalisation
4. Temperature ≥38°C or <36°C measured by any method
5. Informed consent collected on admission or within 48 hours available from guardian/carer

AND at least TWO of the below (with at least ONE of either 1 or 2):
1. Signs of cardiovascular dysfunction: age-related tachycardia or bradychardia or hypotension or need for ≥40 ml/kg fluid resuscitation in first hour after presentation to hospital on day of recruitment
2. Signs of respiratory dysfunction: age-related tachypnoea or brady/apnoea or decreased oxygen saturation (<92% in room air)
3. Skin signs: mottled skin appearance or non-blanching rash or central CRT >2 seconds
4. Neurological signs: irritability, hypotonia, lethargy or an AVPU score V or below

ARI Group Cases:
1. Age <6 years old on the day of admission (day 0) into the study
2. Clinical suspicion of a new episode of acute respiratory tract illness within the last 7 days
3. The attending physician has decided that the child requires hospitalisation
4. Primary reason for hospital admission is clinical suspicion of a new episode of ARI
5. Temperature ≥38°C measured by any method
6. Informed consent collected on admission or within 48 hours available from guardian/carer

AND at least TWO of the below (with at least ONE of 1 or 2):
1. Signs of lower respiratory tract infection: cough, abnormal sounds on chest auscultation (crackles, reduced breath sounds, bronchial breathing, wheezing), dyspnoea (chest indrawing, nasal flaring, grunting)
2. Signs of upper respiratory tract infection: coryza, nasal congestion, sore throat, pharyngitis, myringitis, acute otitis media
3. Signs of respiratory dysfunction: age-related tachypnoea or brady/apnoea or decreased oxygen saturation (<92% in room air)
4. Signs of reduced general state: poor feeding, vomiting, lethargy/drowsiness

CONTROLS:
1. Age < 6 years old on the day of enrolment into the study
2. Afebrile on the day of enrolment
3. No evidence of severe infection as judged by attending physician
4. Informed consent available from guardian/carer

Controls aged < 6 months old will be shared between both groups. Controls should be matched to cases stratified by five age groups (0-3 months, 4-6 months, 7-11 months, 12 months-2 years and 3-5 years) and season (three-monthly intervals starting with January-March). They may be selected from the following patient groups:
1. Attending for an elective or semi-elective procedure requiring general anaesthesia or moderate-deep sedation
(including e.g. surgery, radiological examinations etc)
2. Well and otherwise healthy children attending outpatient clinic for a non-emergency clinical assessment for which a blood test is indicated as part of routine clinical care

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
SLS group: 400 children ≤ 6 months old (at least 300 cases + 52 asymptomatic controls); ARI group: 600 children 0 to 5 years old (at least 320 cases + 268 asymptomatic controls)

Key exclusion criteria
The study will recruit into three groups (SLS, ARI and case-controls), each with different exclusion criteria.

SLS Group Cases:
1. In-patient care for 24 hours or more for any condition within the previous 30 days, except for routine postnatal care
2. Aetiology other than infection (such as trauma, autoimmune disorder, malignancy) is suspected to be the primary cause of the current illness episode
3. Any signs and symptoms suggesting a clear primary focus of infection, such as pneumonia, urinary/kidney infection, open wounds, indwelling catheters, re-activation of previously diagnosed infectious or inflammatory condition
4. Dehydration due to previous illness episode such as diarrhoea and vomiting
5. Immunocompromised infant (stem cell transplant, solid organ transplant, HIV, AIDS, immunosuppressive therapy, inherited or congenital immunodeficiency, haemodialysis)
6. Presence of complex chronic comorbidities
7. Body weight <3kg on day of assessment and/or corrected gestational age <37 weeks

ARI Group Cases:
1. In-patient care for 24 hours or more for any condition within the previous 30 days, except for routine postnatal care
2. Aetiology other than infection (such as trauma, autoimmune disorder, malignancy) is suspected to be the primary cause of the current illness episode
3. Any signs and symptoms suggesting a clear primary focus of infection, such as urinary/kidney infection, open
wounds, indwelling catheters, re-activation of previously diagnosed infectious or inflammatory condition
4. Dehydration due to previous illness episode such as diarrhoea and vomiting
5. Immunocompromised infant (stem cell transplant, solid organ transplant, HIV, AIDS, immunosuppressive therapy, inherited or congenital immunodeficiency, haemodialysis)
6. Presence of complex chronic comorbidities
7. Body weight <3 kg on day of assessment and/or corrected gestational age <37 weeks

Controls:
1. In-patient care for 24 hours or more for any condition within the previous 30 days except for routine postnatal care or current planned hospitalisation/procedure
2. Temperature ≥38.5°C or <36°C
3. Immunocompromised infant (stem cell transplant, solid organ transplant, HIV, AIDS,

immunosuppressive therapy, inherited or congenital immunodeficiency, haemodialysis)
4. Presence of complex chronic comorbidities
5. Body weight <3kg on day of assessment and/or corrected gestational age <37 weeks

Date of first enrolment
15/08/2016

Date of final enrolment
30/06/2018

Locations

Countries of recruitment
England

Estonia

France

Germany

Greece

Italy

Lithuania

Romania

Spain

Switzerland

United Kingdom

Study participating centre
St George's University of London
London
United Kingdom
SW17 ORE

Study participating centre
University of Tartu
Tartu
Estonia
50090

Study participating centre
C.H. Regionaire Universitaire de Lille
Lille
France
59037

Study participating centre
H. U. Robert Debrè. Paris
Paris
France
75019

Study participating centre
National and Kapodistrian University of Athens
Athens
Greece
106 79

Study participating centre
Aristotle University Thessaloniki
Thessaloniki
Greece
541 24

Study participating centre
Universittasklinikum Freiburg
Freiburg
Germany
79106

Study participating centre
Azienda Ospedaliera di Padova
Padova
Italy
2 - 35128

Study participating centre

Ospedale Pediatrico Bambino Gesù
Rome
Italy
4 - 00165

Study participating centre
Vilnius University Children's Hospital
Vilnius
Lithuania
01513

Study participating centre
Victor Babes Clinical Hospital
Romania
030303

Study participating centre
Hospital 12 de Octubre
Madrid
Spain
28041

Study participating centre
Hospital Clinico de Santiago de Compostela
Santiago de Compostela
Spain
15706

Study participating centre
Kinderspital Zurich
Zurich
Switzerland
8032

Study participating centre
Alder Hey Children's NHS Foundation Trust
Liverpool
United Kingdom
L12 2AP

Study participating centre
Great Ormond Street Hospital
London
United Kingdom
WC1N 3JH

Sponsor information

Organisation
Fondazione PENTA Onlus

Sponsor details
Corso Stati Uniti 4
c/o Torre di Ricerca Pediatrica
Padova
Italy
35127

Sponsor type
Charity

Website
http://penta-id.org/

ROR
https://ror.org/00d7mpc92

Funder(s)

Funder type
Government

Funder Name
Seventh Framework Programme

Alternative Name(s)
EC Seventh Framework Programme, European Commission Seventh Framework Programme, EU Seventh Framework Programme, European Union Seventh Framework Programme, FP7

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No