Multi-centre EuRopean study of MAjor Infectious Disease Syndromes (MERMAIDS) - Acute Respiratory Infections

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON50667

Source
ToetsingOnline

Brief title
MERMAIDS-ARI

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Respiratory tract infections

Synonym
flu, Respiratory infection

Research involving
Human

Sponsors and support

Primary sponsor: University of Oxford, contact prof. Peter Horby
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Acute respiratory infections, PREPARE, Prospective observational, RNA expression profiling

Outcome measures

Primary outcome

(1) Identify host and pathogen related determinants of severity of community acquired acute respiratory infections (ARI) in adults. Outcome measures: Differentially expressed host genes (nominal >= 2-fold difference in expression levels) as assessed by RNA transcriptome microarray in hospitalised and primary care managed cases of ARI, stratified by pathogen and comorbidity.

Secondary outcome

(2) Describe the aetiology, clinical management and outcomes of adult patients with community acquired ARI, in both primary care and hospital care, across Europe. Outcome measures: In both groups: Prevalence of detection of putative pathogens in respiratory tract samples. Proportion of cases receiving antibiotics, antivirals, antifungals and/or immunomodulators. 28 day mortality. Additional in group 2 (hospitalised patients): Severity of illness at enrolment as assessed by Pneumonia Severity Index (PSI) and CURB-65. Proportion of cases requiring during admission: supplemental oxygen; non-invasive or invasive mechanical ventilation; extra-corporeal life support. Duration of invasive mechanical ventilation and extra-corporeal life support, if applicable. Proportion of cases requiring Intensive Care Unit (ICU)/High Care Unit (HCU)

admission. Hospital - and ICU/HCU length of stay. In-hospital mortality. Additional in group 1 (primary care): Proportion of cases requiring hospitalisation.

(3) To develop and validate prognostic and diagnostic algorithms. Outcome Measures: This is an exploratory objective. Some measures that could be included in algorithms are classifier gene sets based on host gene expression profiles, pathogen profiles, demographics, co-morbidities, risk factors, and clinical parameters. The diagnostic/prognostic algorithms will be evaluated for their ability to correctly diagnose infecting pathogen and/or predict adverse outcome in ARI.

(4) To gain understanding into pathophysiological mechanisms contributing towards development of severe disease. Outcome Measures: This is an exploratory objective to increase pathophysiological insights by integrative (systems medicine) analyses of pathogen- and patient characteristics. Measures that will be included in these integrative analyses are host gene expression profiles, clinical data on disease progression/outcome, deep sequencing of pathogen genomes and microbiomes.

Study description

Background summary

Based on historic and recent pandemics or pandemic threats, as well as on knowledge of transmissibility and epidemiology, emerging or (re-)emerging

pathogens causing acute respiratory infections (ARI) are considered the most likely candidates to cause the next pandemic.
There is a substantial body of knowledge on clinical risk factors for disease severity and outcome of ARIs. Validated clinical risk stratification tools, such as the Pneumonia Severity Index (PSI) and CURB-65 score predict outcomes and help to guide clinical decision making. Patient groups at risk for developing severe disease are well known, such as the elderly, patients with chronic pulmonary, cardiovascular or metabolic disease or immunocompromised patients. In national guidelines for prevention and treatment of ARI these risk groups are often combined.
However, the underlying pathophysiologic processes that determine the severity of ARI across the diversity of risk groups and pathogens likely differ and are not well understood. This means that within broad phenotypic *risk groups* it is currently not possible to predict who is at increased risk of becoming severely ill. Consequently, there are no opportunities to tailor preventive and therapeutic interventions to individual risk. Personalised or precision medicine is becoming a reality in some areas of oncology, but has yet to enter infectious diseases. In patients that do become moderately or severely ill, there is an assumption that the underlying pathophysiological processes are the same, hence all patients will benefit equally from the same intervention, such as antivirals and immunomodulators. Increased insight into differences in underlying pathophysiological processes across clinical backgrounds and pathogens will open avenues for the development of predictive algorithms that anticipate severity at individual patient levels and direct strategies for individualized therapeutic interventions, hence improving clinical outcomes. Additionally, there may be commonalities in host- and pathogen-related factors that determine outcome which could be used in generic diagnostic (e.g. distinguishing viral versus bacterial infection) and therapeutic approaches. This could be of relevance to the next emerging novel respiratory pathogen, hence contributing to clinical preparedness for a new epidemic threat.
Analysis of the host gene expression profile (transcriptome) provides a high-resolution insight into host responses and pathophysiology, providing opportunities to understand the specific contributions of risk factors, comorbidities and pathogen-specific traits. As an example, human challenge studies using influenza virus, respiratory syncytial virus (RSV) and human rhinovirus (HRV) have indicated that peripheral blood gene expression profiles distinguish between specific viral aetiologies, and symptomatic and asymptomatic influenza virus infection, thus providing valuable insight into the development of clinical disease as well as avenues towards host-targeted approaches of aetiological diagnostics.

Study objective

The primary aim of this study is to identify host and pathogen related determinants of disease severity of ARI. In this study we will include a prospectively defined and sufficiently sized patient cohort that will allow investigations of relative contributions of host and pathogen factors in

development of mild, moderate and severe ARI. The sample size of this study is determined to provide adequate power to identify differences in RNA expression profiles between groups of patients with ARI stratified into groups by major categories of comorbidity (chronic pulmonary/cardiovascular/metabolic disease), and the major causative pathogens (Influenza A, HRV, RSV and Streptococcus pneumoniae). Setting a high bar with regards to sample size, by basing our power calculation on the ability to detect differentially expressed genes between these predefined groups, will ensure the groups will be large enough to also compare less complex determinants of ARI severity, e.g. local and systemic innate and adaptive immune markers, and pathogen markers (e.g. pathogen load). Our analysis will identify differentially expressed genes between patients with different comorbidities within and across ARI aetiologies and severities by combining a fold change assessment (>2-fold nominal change expression levels) combined with a $p<0.05$ correcting for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) < 0.05 in accordance with guidelines from the MicroArray Quality Control (MAQC) group.

Study design

International, multicentre, prospective observational study.

Study burden and risks

This is an observational study with sampling with negligible risks. Nose swabs and venous blood sampling may lead to some discomfort. Blood sampling may cause some pain and bruising. The total amount of blood draw per sampling day is 15ml, with a maximum of 4 sampling days in a period of 28 days. This is acceptable in adults.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Group 1: Hospital
- Suspected of acute respiratory infection, onset of symptoms within 14 days
- Admitted to hospital
Group 2: Primary care
- Suspected of acute respiratory infection, onset of symptoms within 14 days

Exclusion criteria

Group 1: Hospital
- no informed consent
- transfer from another hospital
Group 2: Primary care
- no informed consent
- need for hospital assesment/admission

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2016
Enrollment:	280
Type:	Actual

Ethics review

Approved WMO Date:	12-01-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ISRCTN	ISRCTN18034878
CCMO	NL54834.018.15