Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe

GRACE leaflet

SIXTH FRAMEWORK PROGRAMME

GRACE

Genomics to combat Resistance against Antibiotics in Community-acquired-LRTI in Europe

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Visit our Website

www.grace-lrti.org

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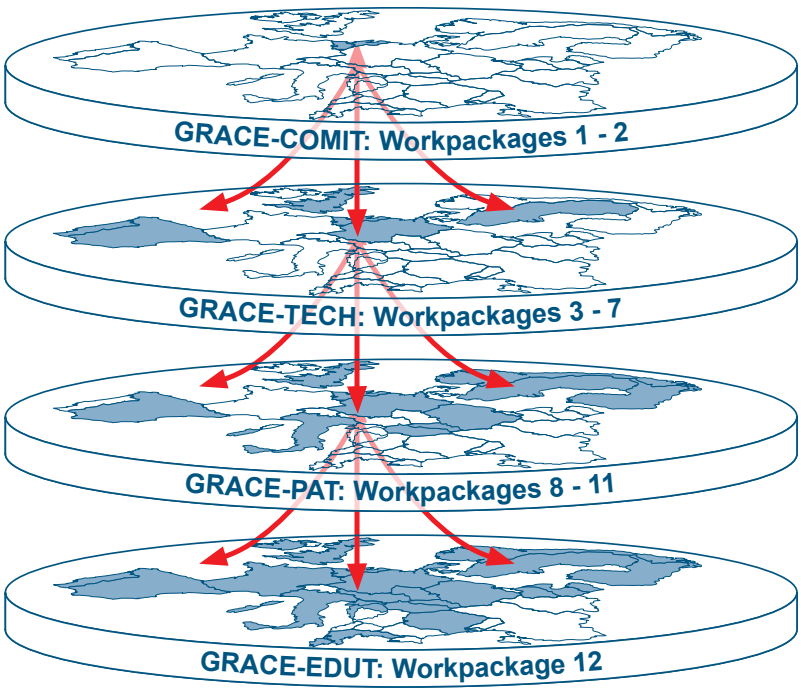
Abstract

GRACE is a Network of Excellence focusing on the complex and controversial field of community-acquired lower respiratory tract infections (CA-LRTI), which is one of the leading reasons for seeking medical care. The promiscuous use of antibiotics to treatment of CA-LRTI accounts for a major part of the community burden of antibiotic use and contributes dramatically to the rising prevalence of resistance among major human pathogens. The overall objective of GRACE is to combat antimicrobial resistance through integrating centres of research excellence and exploiting genomics in the investigation of CA-LRTI. Microbial and human genomics will be integrated with health sciences research consisting of clinical observational and intervention studies, health economics and health education to specifically change practice in managing CA-LRTI.

GRACE is exceptional as it brings together 17 academic groups with a wide spectrum of expertise, spread widely across 9 EU Member States, and 5 SMEs. GRACE will organise professional education, through two leading European scientific societies (European Society of Clinical Microbiology and Infectious Diseases and European Respiratory Society). A high level of co-ordination will be obtained through a professionally IT-supported and rigorous management structure. We are developing a genomic laboratory network in 8 European countries and a primary care research network in 12 European countries during the first 18 months of the project, and then to build on the infrastructure to create the jointly executed research programme. The consortium will become a virtual "European LRTI Research Centre" potentially leading to a forum promoting research and good practice in the field of CA-LRTI.

This research programme has been divided into 4 platforms: GRACE-COMIT, GRACE-TECH, GRACE-PAT, GRACE-EDUT.



Platform description

GRACE-COMIT: Platform for coordination, management and information technology

This platform will develop a high quality organisation and management with a professional IT infrastructure.

Workpackage 1

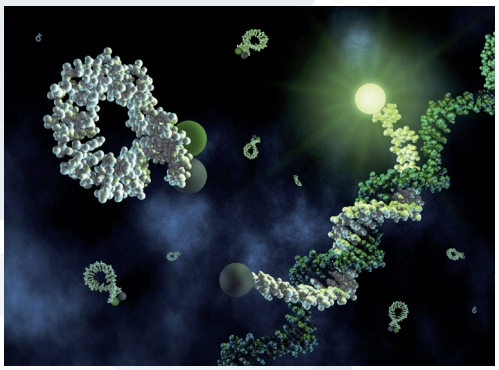
The project management will deal with financial and administrative affairs, internal organisation, confidentiality issues, as well as access, ownership and intellectual property rights. The co-ordinator together with the project management team will ensure compliance with the consortium agreement between the GRACE partners and will monitor the contractual conditions with the European Commission.

Workpackage 2

The IT platform will serve to enter, process, validate and analyse the data retrieved and encountered by the various efforts in microbial and human genomics, as well as in clinical research. A content management system augments the service infrastructure to keep all relevant reports, documents, databases, training materials, etc. accessible for participants of the network.

GRACE-TECH:
Platform for technological developments

Workpackage 3



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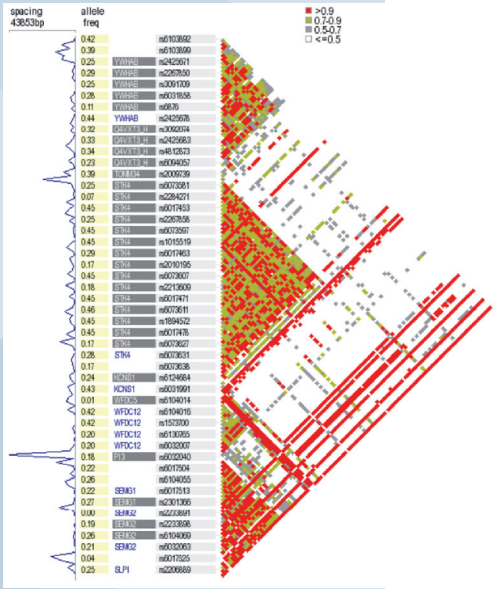
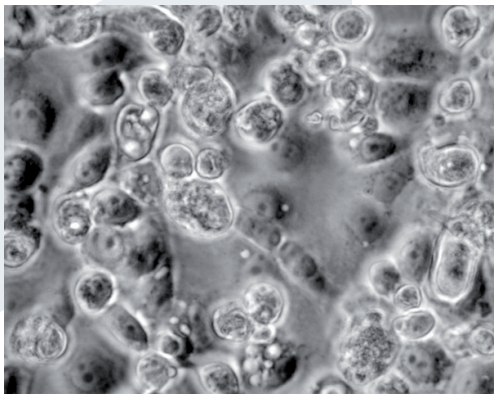
A microbial genomic network of laboratories for diagnostics will develop novel rapid genome-based diagnostic tests for the detection of pathogens and establish a European repository of specimens and strains linked to a database including microbial and patient information.

Workpackage 4



A human genomic network will (i) undertake a large scale genome wide screen for human susceptibility genes affecting severe CA-LRTI and thereby identify potential target pathways for new immunomodulatory approaches; (ii) use human genomic data to devise the potential genetic risk profile and assess whether these polymorphisms identify individuals at risk of various presentations and outcomes in several European populations; (iii) determine whether the human genetic risk factors identified in GRACE interact with each other or with key microbial genetic or other environmental risk factor.

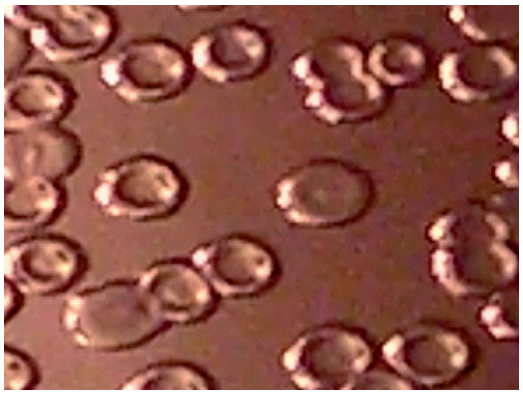
Workpackage 5



New molecular techniques will be developed to detect known or yet unknown viruses in clinical specimens of patients with CA-LTRI. The methods are amplification-based detection assays. High multiple alignments including divergent sequence alignments will be developed and optimised for primer selection.

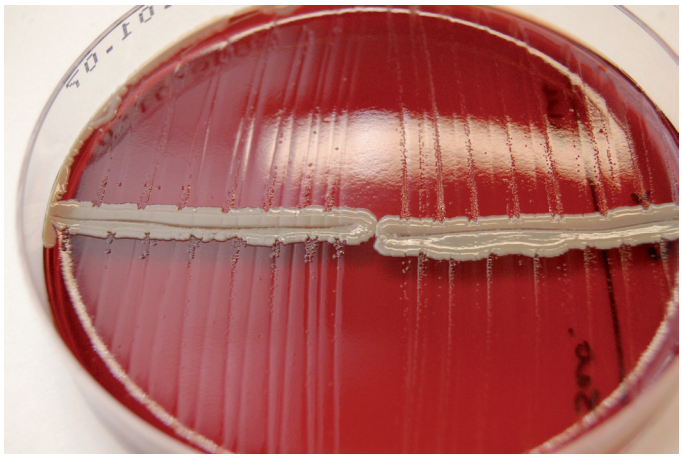
Workpackage 6

A pneumococcal laboratory consortium will (i) correlate antibiotic resistance, virulence characteristics and pneumococcal genotype to severity of CA-LRTI; (ii) perform comparative pneumococcal genomics with micro-array technology with the aim of finding genes important for virulence and for antibiotic resistance development. Animal models will connect the genomic information to the disease kinetics and outcome of CA-LRTI.



Workpackage 7

An *H. influenzae* laboratory consortium will (i) investigate the distribution, transmission and evolution of antibiotic resistance, encoded by non-conjugative and mobile genetic elements; (ii) assess risk factors for infection with resistant *H. influenzae*; (iii) quantify the relationship between the exposure to antibiotics and both the distribution of resistance elements and their population structure.

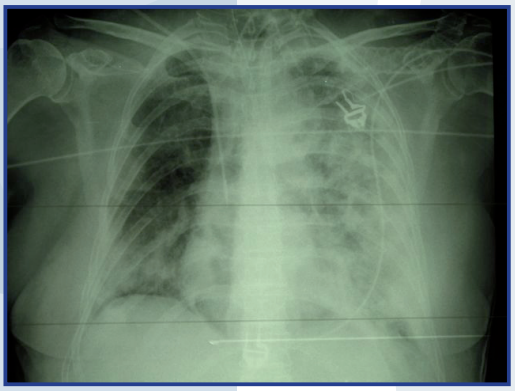


GRACE-PAT: Platform for patient studies

Workpackage 8

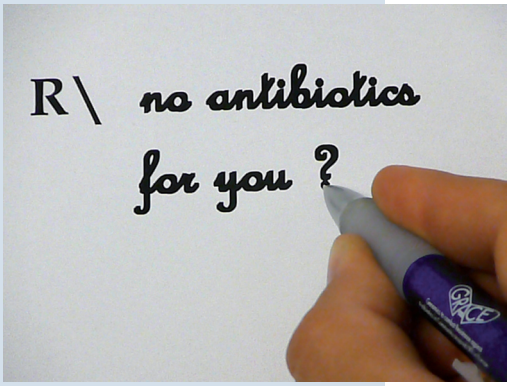
This workpackage will describe current presentation, investigation, treatment and outcomes of CA-LRTI and analyse the determinants of antibiotic use in 14 primary care networks across 12 European countries, using qualitative and quantitative approaches.

Workpackage 9



This workpackage will conduct observational studies on a cohort of several thousands of adults and elderly patients. The aim is to develop models (i) to differentiate viral from bacterial infections; (ii) to detect patients with pneumonia; and (iii) to identify patients at risk for adverse outcomes including severe and prolonged illness.

Workpackage 10



Based on the results obtained in workpackage 8 and 9, on how to change doctor-prescribing behaviour and which subgroups of individuals benefit from antibiotics, respectively, two types of studies will be conducted in this workpackage: a randomised placebo-controlled double-blind trial with patients as unit of randomisation to study the clinical effectiveness of antibiotics in CA-LRTI, and a randomised controlled trial with primary care clinicians' practices as unit of randomisation to study improvements of antibiotic prescribing behaviour.

Workpackage 11

This workpackage will (i) study the economics of molecular diagnostics in CA-LRTI; (ii) model the macroeconomic impact of resistance and policies to contain (iii) model the cost-effectiveness of the management strategies developed in the observational studies; (iv) conduct economic evaluations in parallel with the intervention studies.

GRACE-EDUT: Platform for education and training

Workpackage 12

ESCMID

European Respiratory Society

GRACE-EDUT will aim at spreading knowledge, raising professional and public awareness and providing training on the containment of antimicrobial resistance in CA-LRTI, incorporating new knowledge and competence developed in GRACE. A full repertoire of educational and training initiatives will be developed by the creation of a strong partnership between ESCMID and ERS. This platform will develop educational packages including web-based resources and workshops to inform postgraduate lifelong learning needs of prescribing professionals.

POTENTIAL APPLICATIONS

- Novel rapid genome based diagnostic tests for the detection of pathogens implicated in CA-LRTI.
- A European repository of specimens and strains linked to a database including microbial and patient information.
- Risk factors for infection with resistant *S. pneumoniae and H. influenzae* in patients with CA-LRTI.
- Pneumococcal genes important for virulence and for antibiotic resistance development.
- Optimal pneumococcal treatment and prevention strategy linked to severity of CA-LRTI.
- Human susceptibility genes affecting severe CA-LRTI.
- Potential human target pathways for new immunomodulatory approaches.
- Potential genetic risk profiles for various presentations and outcomes of CA-LRTI in several European populations.
- Evidence-based definitions of the major CA-LRTI.
- Clinical outcome measures for evaluating interventions.
- Clinical models to differentiate viral from bacterial infections and identify pneumonia.
- Clinical models to identify patients at risk for adverse outcomes including severe and prolonged illness.
- Subgroups of patients with CA-LRTI which benefit and which do not from antibiotic treatment.
- Practice based intervention in reducing inappropriate antibiotic use and resistance in patients with CA-LRTI.
- Cost-effectiveness of the management strategies developed in the observational and intervention studies.
- A model for the macroeconomic impact of antibiotic resistance and policies to contain resistance.
- Economic evaluations of molecular diagnostics.
- Educational packages to inform postgraduate lifelong learning needs of prescribing professionals.

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