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

GRACE news

Spreading Excellence in Respiratory Tract Infections

October 2009, Volume 4 (4)

Editorial

Paul Little and Theo Verheij

Opportunities, threats and new horizons for the GRACE ship

The GRACE Network continues to prove just how capable it is. The third season is upon us, and the primary care networks (PCNs) are already showing that the third season should be a great success: several Networks started before October and we have already gone past 4000 patients and controls recruited with high quality clinical data and microbiology. This is an astonishing achievement - it really is an honour to be part of this consortium.

So is it plain sailing from now on, or are there some rocks below the surface which threaten to sink the GRACE ship? The major potential reef is the swine flu pandemic. Although on the one hand GRACE provides us as clinicians and researchers a fantastic opportunity to learn more about the H1N1 virus - its natural history, clinical presentation, and how these differ from other viral and bacterial aetiologies - the pandemic also provides significant threats, mainly threats to recruitment. Primary care services may either being swamped with patients, or fail due to illness among practice staff, or may not see patients with cough due to changes in national policies of presentation algorithms (e.g. in some countries patients with cough and pyrexia are instructed not to attend). However some PCNs have dedicated staff which should actually facilitate recruitment, and others are using techniques to minimise the impact such as recruiting one patient per week per GP; furthermore the major adverse effect of the pandemic should only last 6-8 weeks at the peak of the surge, so even in PCNs adversely affected recruitment during the rest of the seasons should be possible. The other threat is the limited recruitment to date into the trial as opposed to the observational study, but the recruitment balance to the trial in season two improved considerably and with similar improvement in season three the trial should also reach important targets. It will require all the enthusiasm, determination, cooperation and collaboration shown so far in the GRACE Network to achieve its ends in season three, but at the great meeting in Cardiff hosted by Chris Butler and his team the PCN coordinators and facilitators demonstrated just these qualities.

It is easy to just concentrate very hard on season three and perhaps that is right for the moment, but for those pondering the deep questions of life such as…'Is there life beyond season three?' we can answer a most definite 'Yes'! During season three in coordination with the CHAMP project we will be developing an intervention to help GPs appropriately reduce antibiotic use and which will be finalised to incorporate the wealth data coming from CHAMP and from GRACE, e.g. WP8, WP9 and WP10a. We will be approaching PCNs to consider participating in the second trial and also collecting some baseline audit data prior to intervention in season four. Like the first trial of WP10, the second trial will also be a first - an international randomised controlled trial with a quality assured intervention to change antibiotic prescribing behaviour.

Meanwhile as you think about the GRACE ship sailing into new uncharted territories, we wish the PCNs the best of luck in recruitment in season three and look forward to a chilly meeting in Poland where hopefully an ice breaker will not be needed for the good ship GRACE!

Paul Little
Theo Verheij

Table of content

News

GRACE WP9-10: The final countdown!

Are we ready to start the third and final season? Will we be able to make it a success? I think both questions can be answered with a resounding YES. On Friday, 25th of October the GRACE National Network Facilitators (NNF) and Coordinators (NNC) met in Cardiff to discuss how to optimize the conditions for a successful final WP9-10 season. Almost all networks were represented. Also the GRACE management team was there at full strength, ready to share their vision of how to bypass possible obstacles and to provide us with clear answers to any questions. So at 8:30 in the morning, everyone was there to support the start of our final season.

The starting point: After season two, 3962 patients and controls were recruited out of our final target of 6000, leaving a little over 1000 GRACE patients & 1000 controls to go (Figure 1). In other words, an additional 1/3 are left to include in the third season. This sounds feasible, especially since all networks are ready to recruit from day 1 of this season. This was not the case in previous seasons. In the meantime we have already passed the milestone of the 4000th inclusion, with 4006 patient in, and 6 of the 16 networks already actively recruiting on the 1st of October. Some of the primary care networks (PCNs) did not feel the need to have a summer stop at all.

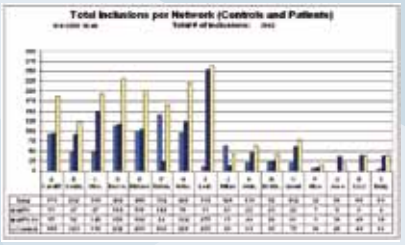


Figure 1

Also the percentage of patients in WP10 (patients taking the study medication: amoxicillin or placebo) compared to those only participating in the observational part of the study (WP9) is improving (Figure 2). In season one 52% of the patients were recruited for both WP9 and 10. In season 2 we managed to reach 67%. And after our workshop 'How to improve your WP10 recruitment' and sharing our experiences in Cardiff, we expect to do even better.

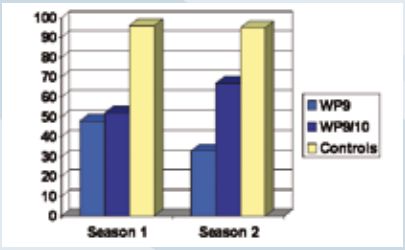


Figure 2

Another advantage for the coming season is the large group of experienced GRACE GPs spread all over our 16 PCNs in 12 countries within Europe, from North to South, and from East to West. Over 500 GPs are trained and 212 of them have proven their dedication to GRACE by actively recruiting patients. Some of them even managed to recruit over 100 patients on their own. Amazing! And the group of GRACE GPs is still growing. PCNs are trying to find new GPs on an ongoing basis to expand their recruitment capacity. An activity that can be monitored closely using GOS, the GRACE Online System. This system is of great help to all of us, making it easy to execute and monitor the different activities going on within the networks, from recruitment to data entry. It also provides us with individual task lists and databases for analyses. GRACE could not be managed as smoothly as it is now, without GOS and of course the people behind the system.

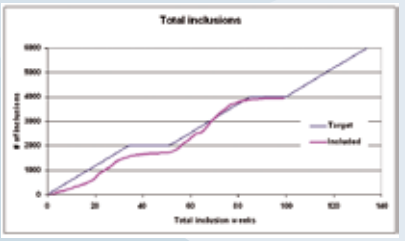


Figure 3

And what about risks? Of course there are risks. Some of them are standard, like maybe losing interest after two seasons of searching for GRACE patients and controls. Others are unexpected, like the H1N1 pandemic we will have to deal with. But at the same time this situation will give us the once in a lifetime opportunity to collect a unique set of flu pandemic related data in the unique setting of GRACE PCNs. We have to deal with threats and risks, like we have done before and we have contingency plans in place. And of course we always have to keep in mind the Antwerp-rule: Just 1 (one) patient or control per week per GP, with an additional 15 minutes of work, will do the job. So as long as we all do it together, meeting the target should be possible (Figure 3).

It is certain that coughing patients will appear again. I am sure we are only one season away from writing (GRACE) history. Everyone is ready to go. We only have to make it happen. Let the countdown begin…

Good luck to all of you and let's do it.

Curt Brugman
Gilly O'Reilly

WP11 Update: Economics need clinical input

In recent months the WP11 team in Birmingham has been focused on the analysis of the economic aspects of the GRACE WP8 data. Initial analysis of the cost of LRTI care across the GRACE networks has been completed and a paper from this work has just been submitted for publication. Further work in two areas has continued: (i) assessing the impact of valuing EQ-5D data with different tariffs; and (ii) assessing the cost-effectiveness of CRP testing. Results from the latter piece of work were presented at the September GRIN conference in Cardiff. Preparatory work for the analysis of the WP9 and WP10 data has also begun and as part of this we will, later this year, be contacting network and workpackage leaders to obtain additional information to aid the economic analysis of the WP9 and WP10 data.

The WP11 team at LSHTM has been working on the macroeconomic model, and preparation of the macroeconomic model for comparative static analysis has gone well. Data templates to facilitate production of a social accounting matrix from raw economic data have been prepared. Mathematical programs to balance the social accounting matrix and reconcile shortcomings in the input-output data are also drafted so the tools for analysis are on schedule. The main shortcoming for the modelling is still the absence of any specified pattern of resistance over time or a clear relationship between prescribing and resistance. One GRACE partner has supplied some studies of broad interest, but we are still lacking an antibiotic resistance parameter input for the model that supersedes the data presented in Milan last March. Further input from GRACE partners is requested to assist in the aspects of this work that transcend economics.

Raymond Oppong
Marcus Keogh-Brown

Abbott
A Promise for Life

Luminex

WP 3: Abbott supports studies for the detection of respiratory viruses in GRACE

Over the past 10 years, nucleic acid amplification tests have been developed for a number of respiratory viruses. Nucleic acid amplification tests, including PCR and nucleic acid sequence-based amplification (NASBA), have shown greater sensitivity than the conventional methods such as DFA and culture. Multiplex PCR assays have been used to detect the presence of one or usually more respiratory virus infections in respiratory tract specimens in one or more reactions. The emergence of five new respiratory viruses since 2000, including metapneumovirus (MPV), severe acute respiratory syndrome coronavirus (SARS-CoV), avian influenza virus H5N1, CoVs NL63 and HKU1, and human bocavirus, has presented challenges for the virology laboratory and increased the need for diagnostic tests to detect these emerging viruses.

Luminex has developed a multiplex PCR assay, called the The xTAG® Respiratory Viral Panel test, that can detect 20 different respiratory virus types/subtypes in a single 5-h test, including the conventional respiratory viruses influenza A and B viruses, parainfluenza virus types 1 to 4, RSV, adenovirus, MPV, common cold viruses such as rhinovirus, CoVs OC43 and 229E, and newly emerging respiratory viruses, such as SARS-CoV, avian influenza virus H5N1, and CoVs NL63 and HKU1, which usually are not tested for by clinical laboratories. The test uses a 96-well microtiter plate format and the Luminex 100 flow cell instrument. Following nucleic acid extraction, the RVP assay takes about 5 h to perform, making it possible to provide same-day results. The Luminex xTAG RVP assay has recently been approved by the FDA for the most common viral targets and is now commercialised by Abbott.

We discussed with Abbott on the use of Luminex xTAG RVP assay on GRACE samples. They showed interest in this European multicenter study and offered to provide us a considerable number of assays for the detection of the included respiratory viruses. We will compare the detection of respiratory virus targets using the Luminex xTAG respiratory viral panel (RVP) assay with our individual real-time NATs used in GRACE.

This is again an important financial support for GRACE which will enable us to evaluate the sensitivity and the specificity of this rapid 5 hour tests for the detection of respiratory viruses compared to our in-house developed tests and will allow us to collect epidemiological information on the importance of the detected viruses in an outpatient setting attending general practitioners.

Greet Ieven

GRACE Related Projects: *SATURN*

SATURN will study the impact of antibiotic exposure on antimicrobial resistance (AMR) with a multidisciplinary approach that bridges microbiological, clinical, epidemiological and pharmacological research. SATURN will improve methodological standards and conduct research to better understand the impact of antibiotic use on acquisition, selection and transmission of antibiotic-resistant bacteria (ARB) in different environments, by combining state-of-the-art analyses of molecular, ecologic and individual patient-level data. The proposed program and anticipated results will help reduce the burden of AMR in Europe and guide both clinical decision making and policy decisions in this area.

SATURN (Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria) is an FP7 Collaborative project (Grant agreement number: 241796) that responds to an urgent need, as stated in the EU Council conclusions (June 2008) on AMR, in which the EU "*stresses the need of research in the area of AMR, e.g. to increase the understanding of the mechanisms and underlying risk factors that advance the development of AMR and to increase the knowledge of the effectiveness of current and future control measures.*"
AMR is rampant among bacteria that cause healthcare- and community-acquired infections, driving up costs and increasing the difficulty of therapeutic management. To gain a handle on the factors that are propelling the problem of AMR, molecular and patient-level investigations are necessary to better elucidate the time-varying and heterogeneous role of antibiotic selection pressure on emergence and selection of AMR.

This five year and 6 million euro project that starts early 2010 aims at defining strategies to improve the knowledge about antibiotic selection pressure and judicious antibiotic use. One intervention study and three observational clinical studies will be conducted that will produce demonstrable improvements over previously generated evidence regarding the effect of antibiotic exposure and selection pressure on acquisition, selection and transmission of ARB within hospital and community settings. Molecular and pharmacologic issues generated by the four clinical studies will be also addressed.

The research program will provide a comprehensive knowledge base on the effect of various antibiotic classes, duration of treatment, order of treatment and dosage used on AMR in the community, general hospital wards and in intensive care units. This comprehensive data will be generated at the individual level for both colonised and non-colonised patients and at the ecological (i.e. ward) level. Moreover, SATURN will provide data on the effects of antibiotics on resistance both at the human host level and at the bacteria level. Combining the results of epidemiological investigations with microbiological and molecular studies on epidemicity, virulence and fitness of strains will provide data for action. Thus, SATURN results will provide the basis for better treatment decisions regarding antibiotic choices in various settings to minimise AMR, without compromising patient outcomes. This unprecedented approach will allow development of guidelines on antibiotic use and formulary interventions at the local, regional and European level.

The gaps between scientific knowledge and current practices of misuse of antimicrobial agents are enormous. AMR represents a particular challenge, because it touches upon several aspects of care, from basic knowledge to antibiotic prescribing. The continuing emergence of new resistance traits or their spread to new species and new epidemiological chains permanently challenges our ability to contain AMR. SATURN will address this knowledge gap through a variety of research platforms focusing on the effect of various antibiotic agents and prescribing patterns on selection and spread of ARB. The ultimate aim is therefore to develop an educational knowledge base for better antibiotic prescribing practices reflecting the best of current knowledge. Links to the resources of the European professional societies relevant to the objectives (ESCMID, ESICM, ESPRM) and the existing networks (ESAC, EARSS) will allow to develop educational material. An integrated and structured repertoire of educational and training activities will be developed that will be made available for the training of clinicians scientists, infection control personnel and other relevant health care professionals, as well as for the public.

Stephan Harbarth

Coordinator:
Dr. Stephan Harbarth
Université de Genève
Geneva, Switzerland

Partners:
Dr. Johan Mouton
Stichting Nijmeegs Interkonfessioneel Ziekenhuis Canisius-Wilhelmina (Canisius Wilhelmina Hospital)
Nijmegen, Netherlands

Dr. Maciek Godycki-Cwirko
Universytet Medyczny w Lodzi (Medical University of Lodz)
Lodz, Poland

Prof. Yehuda Carmeli
The Foundation for Medical Researchinfrastructural Development and Health Services next to the Medical Center (Tel Aviv Tel-Aviv Medical Center)
Tel Aviv, Israel

Prof. Herman Goossens
Vaxinfectio
Universiteit Antwerpen
Antwerpen, Belgium

Prof. Evelina Tacconelli
Universita Cattolica del Sacro Cuore
Milano, Italy

Prof. Marc Bonten
Universitair Medisch Centrum Utrecht
Utrecht, Netherlands

Mr Carlos Triay
ARTTIC
Paris, France

Prof. Jordi Vila
Consorci Institut d'Investigacions Biomediques August Pi i Sunyer
Barcelona, Spain

Prof. Laurent Gutmann
Groupe Hospitalier Paris Saint Joseph
Paris, France

Dr. Knut Ohlsen
Julius-Maximilians Universität Würzburg
Würzburg, Germany

Dr. Biljana Jovanovic
Clinical Center Of Serbia
Belgrade, Serbia

Dr. Smaranda Botea
Institute Infectious Diseases Bals
Bucharest, Romania

Spreading excellence in respiratory tract infections:

Pneumococcal conjugate vaccination: a valid solution for bacterial resistance?

At the GRACE Workshop held in Cambridge in September 2008, Åke Örtqvist reviewed the key issues relating to the prevention of pneumococcal disease. You can find his full presentation with audio freely available on the GRACE e-learning platform (www.grace-edut.org). Here he reviews the latest data to emerge in this fast moving area.

During the last 30 years of the 20th century, pneumococcal resistance increased rapidly world-wide. Around the year 2000, about half of all pneumococcal strains causing invasive disease in the U.S. and many other countries were resistant to penicillin and/or macrolides.

In 1999 the 7-valent pneumococcal conjugate vaccine (PCV7) was included in the general immunization program of children in the U.S. The serotypes included in PCV7 were, 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes were chosen because they were the most prevalent ones among children, as well as the ones most often associated with pneumococcal resistance. PCV7 has been shown to significantly reduce nasopharyngeal carriage of vaccine-type (VT) pneumococci. However, at the same time non-vaccine-type (non-VT) strains and to some extent vaccine-related (VRT) strains, e.g. 6A and 19A, have increased resulting in carriage rates overall of similar magnitude as pre-PCV7.

The initial effects of PCV7 on invasive pneumococcal disease (IPD) in vaccinated children in the U.S. was enormous, with a near elimination of VT-disease and a reduction of IPD overall, by 70-80%. There has also been a significant indirect effect of the vaccine, with reduction of IPD both in infants to young to be vaccinated and in adults. Since the VTs were those most often associated with high-level penicillin-resistance, the reduction of VTs was followed by a significant reduction of IPD caused by penicillin non-susceptible pneumococci (PNSP). In addition pneumococcal vaccination of children has been shown to lead to a reduced antimicrobial usage due to a lowered burden of pneumococcal disease, which in turn may reduce selection pressure and antimicrobial resistance.

Over time, however, serotype replacement with non-VT's and VRT's has led to a new increase of PNSP. The replacing VRTs and non-VTs have most often been intermediately pencillin-resistant, but there has also been an increase in intermediate resistance among these serotypes. In addition, fully resistant clones of serotype 19A have emerged and increased significantly; 19A is currently the dominant serotype among children under 5 years of age in the U.S.

In conclusion, the widespread introduction of vaccination of children with PCV7 is likely to initially reduce high-level drug-resistance in *S.pneumoniae.* However, over time the reduction of VTs will lead to a serotype replacement with VRTs and non-VTs and a new increase in resistant pneumococci. However, in the long run antibiotic pressure is probably an even more important driver of highly drug-resistant pneumococci. Therefore, it is not only important to reduce inappropriate antibiotic, but also to expand the current PCV7 to PCV13 as soon as possible, since the latter vaccine adds serotypes 1, 3, 5, 6A, 7F, and19A. It will also probably be necessary to regularly introduce a new conjugate vaccine with changed and/or broader coverage, say every 5-10 years. In the future a vaccine based on antigen/antigens common for all pneumococci might reduce the circulation of drug-resistant pneumococci.

Åke Örtqvist

References

1. Talbot TR, Poehling KA, Hartert TV, et al. Reduction in high rates of antibiotic-nonsusceptible invasive pneumococcal disease in Tennessee after introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2004; 39: 641-8
2. Hennessy TW, Singleton RJ, Bulkow LR, et al. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. Vaccine 2005; 23: 5464-73
3. Pai R, Moore MR, Pilishvili T, et al. Postvaccine genetic structure of Streptococcus pneumoniae serotype 19A from children in the United States. J Infect Dis 2005; 192: 1988-95
4. Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med 2006; 354: 1455-63
5. Cohen R, Levy C, de La Rocque F, et al. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use on nasopharyngeal carriage of nonsusceptible pneumococci in children with acute otitis media. Ped Inf Dis J 2006; 25: 1001-07
6. Farrel DJ, Klugman KP, Pichiero M. Increased antimicrobial resistance among non-vaccine serotypes of Streptococcus pneumoniae in the pediatric population after the introduction of 7-valent pneuococcal vaccine in the United States. Ped Infect Dis J; 26: 123-8
7. Hanage WP, Huang SS, Lipsitch M, et al. Diversity and antibiotic resistance among non-vaccine serotypes of Streptococcus pneumoniae carriage isolates in the post-heptavalent conjugate vaccine era. Clin Infect Dis 2007; 195: 347-52
8. O'Brien KL, Dagan R, Mäkelä PH. Nasopharyngeal carriage. In: Siber GR, Klugman KP, Mäkelä PH, editors. Pneumococcal Vaccines. The Impact of Conjugate Vaccines. Washington, DC: ASM Press, 2008: 279-300
9. Dagan R, Klugman KP. Impact of Conjugate Pneumococcal Vaccine on Antibiotic Resistance. In: Siber GR, Klugman KP, Mäkelä PH, editors. Pneumococcal Vacccines. The Impact of Conjugate Vaccines. Washington,DC: ASM Press, 2008: 369-85
10. Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. Lancet Infect Dis 2008; 8: 785-95

WP12: GRACE Educational Workshop at ECCMID 2009

The 6th GRACE Postgraduate Course at the European Congress of Clinical Microbiology and Infectious Diseases(ECCMID) 2009 - designated an Educational Workshop - was an outstanding success with some 120 delegates attending and discussing the presentations on the theme of "Challenges and change in pneumonia: focus on *Streptococcus pneumoniae* and community-acquired MRSA". The spring sunshine that bathed Helsinki for the duration of the Congress gave an added lift to the spirits of all attending. Chaired by Javier Garau (at that time President-elect of ESCMID) and Roger Finch (Co-chair of GRACE WP12) the Workshop dealt with many of the complex and evolving issues pertaining to the epidemiology, diagnosis, clinical impact and management of community-acquired pneumonia (CAP) by *Streptococcus pneumoniae,* the leading respiratory tract pathogen, and community-acquired MRSA, now well established in North America and emerging in Europe.

Ron Dagan (Israel) reviewed the impact of pneumococcal conjugate vaccines (PCVs) on childhood pneumonia and lower respiratory tract infections (LRTIs). He emphasised that PCVs had had both expected and unexpected effects on the incidence and nature of pneumococcal disease. In children, there has not only been a significant impact on invasive pneumococcal disease but also on LRTI, traditionally considered non-pneumococcal in nature. He emphasised that high rates of vaccine uptake are necessary to ensure maximum herd benefit. Serotype shift, as a consequence of PCV, has resulted in the need to broaden the serotype spectrum of future PCVs.

Ake Ortqvist (Sweden) complemented the first presentation by discussing the herd effect of PCV on adult LRTI. This thoughtful review analysed the relative immunogenicity of PCVs. The impact in adults of the 7-valent PCV based on US data and more recently early European data, is favourable, but largely restricted to vaccine serotype disease, notably bacteraemic pneumococcal pneumonia. When looked at in terms of hospitalisation rates pre- and post-PCV7 use, the international literature gives a mixed picture.
The changing nature of pneumococcal lung disease has inevitably impacted on therapeutic management. Javier Garau led the delegates through the evolution of drug resistance in pneumococcal disease to beta-lactams, macrolides and the fluoroquinolones. This was followed by a thoughtful analysis of evidence relating to the pros and cons of combination versus monotherapy for the treatment of CAP.

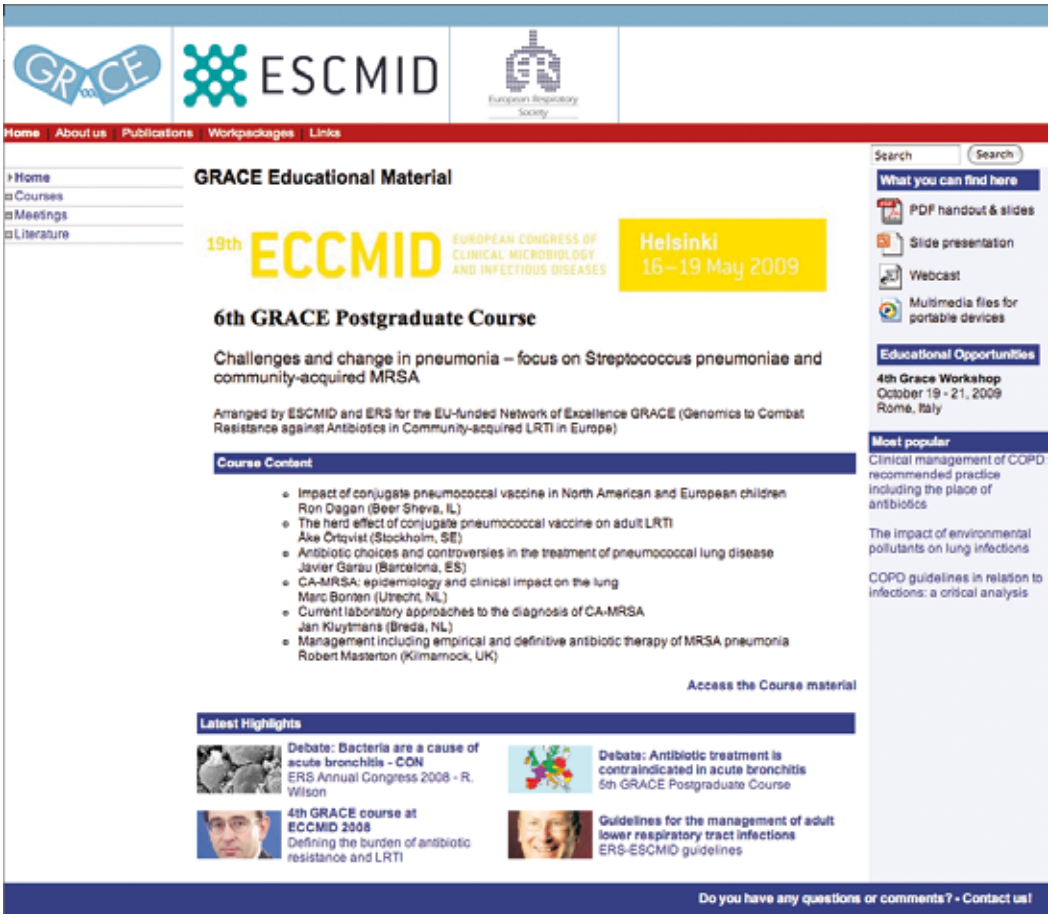
The second part of the workshop focused on community-acquired MRSA. An excellent review of the epidemiology, carriage, virulence factors and antibiotic resistance issues from genetic to clinical impact, was given by Mark Bonten (Netherlands). The nature and effectiveness of de-colonisation regimens was also touched on. The need for good surveillance of community MRSA was emphasised in order to inform policy and management.

In an excellent review of the laboratory detection of MRSA, Jan Kluytmans (Netherlands) defined the rationale and range of methodologies for identifying MRSA. An analysis of the strengths and weaknesses of rapid diagnostic approaches was particularly valuable. At present, the balance between rapid and conventional detection approaches is largely influenced by the clinical need for treatment or prevention of MRSA infection.

Bringing the focus back to the lungs, Robert Masterton (UK) discussed the current and emerging therapeutic approaches to the treatment of MRSA pneumonia. He approached this by reviewing the serious nature of MRSA pneumonia, whether it be hospital or community-acquired. While vancomycin plays a pivotal role in treatment its efficacy is being undermined by "MIC creep". The effectiveness and place of new agents, such as linezolid, was thoroughly discussed.

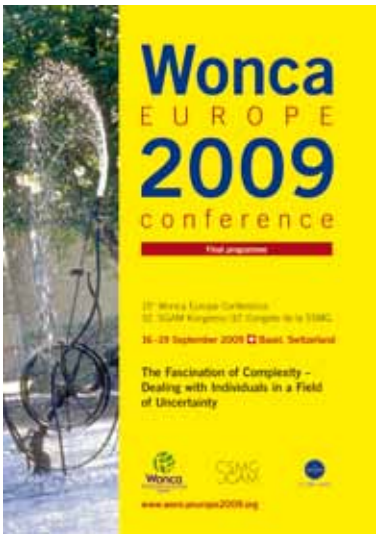
The presentations and supporting literature for all presentations are freely available on the GRACE educational portal (www.grace-edut.org) which has been designed by Work Package 12 on behalf of the GRACE network in collaboration with the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).

Roger Finch



Spreading GRACE news

All stages of research projects are fun and challenging, but the most rewarding is to analyse results, and discuss these results with colleagues. Though we are still very busy with collecting data and preparing next steps within GRACE, thrilling results from workpackage 8 are now being analysed and the first results are presented!



At WONCA Europe 2009, a European conference of general practitioners, in Basel in September Kerry Hood presented on diagnostic procedures in patients with LRTI in Europe for a full conference room and had lots of positive reactions from the audience. And the GRACE newsletters available at the back were all taken home by participants!

One week later there was of course the yearly meeting of the General practice Respiratory Infections Network (GRIN) in Cardiff. The meeting was combined with a meeting of all coordinators and facilitators of the GRACE primary care networks in WP9-10. And almost everybody was there! We had a very stimulating and helpful discussion, and presentations on tips and tricks to enhance inclusion rates and face the influenza pandemic during our third season. The vast majority of network colleagues stayed for the GRIN meeting and that was a wise decision! Wonderfully hosted by Chris Butler and his team, we had a fantastic array of presentations, keynote lectures and discussions on latest research results and visions on respiratory tract infections and antibiotic use in primary care. There was a set of four presentations on new GRACE results: Maciek presented a comparison on sickness certifications in Poland and Norway, David Gillespie presented interesting data on follow-up of patients, Ray Oppong talked on the cost-effectiveness of CRP testing and Samuel Coenen on (perceived) patients expectations towards treatment of LRTI. The data were very interesting, the discussions were lively and stimulating. Among the audience were also colleagues from Australia, Canada and the USA, so next to our BMJ paper, the fame of GRACE will now also be spread by live witnesses!

Apart from presentations of study results, our colleagues from WP12 of course still are organising educational meetings. During the ERS conference we had a very successful and high standard postgraduate course on prevention of LRTI and there will be a highly interesting workshop on the aetiology, diagnosis and treatment of LRTI in primary care on October 23 and 24 in Rome! (see also http://dev.ersnet.org/)

So both from a research as a educational point of view, GRACE is really spreading the news!

Theo Verheij

Colophon

Design
Nieuwe Media Dienst
Universiteit Antwerpen

Editorial team
Samuel Coenen
Roger Finch

Contributors
Francesco Blasi
Curt Brugman
Samuel Coenen
Roger Finch
Stephan Harbarth
Marcus Keogh-Brown
Paul Little
Greet Ieven
Raymond Oppong
Gilly O'Reilly
Åke Örtqvist
Theo Verheij

GRACE project leader
Herman Goossens
University of Antwerp - CDE
Laboratory of Microbiology
Universiteitsplein 1
2610 Antwerp
Belgium
www.grace-lrti.org