

Editorial

TRACE & PREPARE

TRACE is involved in PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics), an FP7 project proposal submitted and granted in response to HEALTH.2013.2.3.3-1. "Clinical management of patients in severe epidemics".



As society becomes more sophisticated, technology-based, urbanised and connected, microbes adapt and find new opportunities. Therefore, infections with epidemic potential remain a threat to human health. Much progress has been made in the design and development of appropriate structures and procedures for rapid and adequate Infectious Diseases (ID) outbreak public health response measures, by national and international health authorities. Likewise, preclinical research responses to severe ID threats and outbreaks by the scientific research community (e.g., epidemiological, microbiological, immunological and genetic research) has also made important progress during the last decade in terms of the ability to respond rapidly. This is in sharp contrast to the clinical research response, which is often delayed, isolated and fragmented, having - as a consequence - little to no impact on improving patient outcomes and developing high-quality evidence to inform clinical management strategies. Indeed, we lack the co-ordination and clinical tools that are required to respond rapidly to new threats. PREPARE will streamline our response, link primary and secondary clinical care with public health and basic science to undertake research in the inter-epidemic period, detect outbreaks with epidemic potential and activating dynamic investigation teams, deploying shared resources across Europe to mitigate the impact of future epidemics on Europe's health, and economic integrity.

PREPARE will transform Europe's response to infectious disease and future epidemics by providing infrastructure, co-ordination and integration of existing clinical research networks with public health. These large, well-established clinical networks (GRACE and its successor TRACE in primary care; COMBACTE, CAPNETZ, SERGAS, PENTA, ICU-ESICM network in hospital care), provide PREPARE with an operational 'up-and-running' clinical research infrastructure that has a proven capability to recruit large numbers of patients across the full clinical spectrum of ID syndromes. In PREPARE, we will conduct observational and interventional cohort studies and randomised clinical trials, in children and in adults. For this, we will develop pre-emptive solutions to ethical, administrative, regulatory and logistical bottlenecks that prevent a rapid response in the face of new threats. We will investigate the pathogenesis of relevant infectious diseases and accelerate the development of state-of-the-art near-patient diagnostics. Finally, we will provide education and training not only within PREPARE, but to opinion leaders, funders and policy makers, thereby streamlining future outbreak responses. By strengthening and integrating the European clinical elite with pre-clinical and public health research ID research, PREPARE will result in a highly effective response to any future outbreaks based on solid scientific advances and global leadership. The PREPARE project is funded with a grant of 24 Million EUR by the 7th Framework Programme of the European Commission for a period of 5 years, starting 1 February 2014. The kick-off meeting will be held 5-7 February 2014 in Antwerp, Belgium.

Table of content

- p. 1 **Editorial**
- p. 2 **News**
- p. 3-7 **Spreading excellence in respiratory tract infections:**
- p. 8 **Third Steering Committee Meeting and sixth ESF Science Meeting**

Herman Goossens
Coordinator PREPARE
Laboratory of Medical Microbiology, VAXINFECTIO
University of Antwerp, Belgium

New ESF Science Officer for TRACE

In August 2013, our ESF Science Officer Dr. Kirsten Steinhausen, announced that she handed over the scientific coordination of TRACE to Dr. Maria Manuela Nogueira. Dr. Maria Manuela Nogueira is a very experienced senior science officer at ESF. Dr. Kirsten Steinhausen has taken a new position as a Professor for Applied Public Health in Furtwangen, Germany, but she will continue working as a consultant for ESF.

New TRACE members

TRACE welcomes the University of Oslo (Norway), represented by Morten Lindbæk, as a new TRACE member. On the other hand, the *Fundacja Centrum Mikrobiologii* (CMK, Poland) is no longer supporting TRACE. This means TRACE receives support from 22 GRACE and other partners next that from 8 ESF Member Organisations.

Heiner Bucher of the Basel Institute for Clinical Epidemiology & Biostatistics (Switzerland) succeeds Kathrin Mühlemann to represent the Swiss National Science Foundation.

TRACE @ ECCMID 2013

A TRACE poster was presented at the European corner of the ECCMID 2013 held in Berlin from 27 to 30 April 2013. The March 2013 issue of TRACE News and the TRACE Leaflet were distributed among the more than 9900 delegates.

TRACE

Translational Research on Antimicrobial resistance and Community-acquired infections in Europe

Summary

Opportunities in infectious disease management have resulted in prescriptive penicillin, which largely explains the escalating antibiotic resistance of common bacterial respiratory pathogens in the community. Technologies and solutions are available to address this issue, and the individual areas of expertise do exist in Europe, but the problem is in integrating these.

Therefore, TRACE was launched on June 18, 2011, in Antwerp, supported by ESF (European Science Foundation), 17 GRACE (Science) to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (www.grace-ri.eu) and 8 other partners. TRACE aims to consolidate the expertise integrated in several research programmes, in particular within the GRACE Network of Excellence, beyond EC funding, and to apply it to steer ongoing and to display new research activities, and to disseminate its results.

GRACE has been a unique and successful Network of Excellence encompassing 20 Primary Care Networks in 15 EU countries, human and microbial genetics, collaboration with the major infectious disease and primary care societies, SMEs, integrated by means of state-of-the-art ICT. The GRACE concept serves as a model for TRACE aiming to complement the ongoing activities substantially.

TRACE produced a brochure, a website and a newsletter. To disseminate the results of GRACE, but also of other EU funded projects like CHAMP (www.champ-antibiotics.org) and IMPIV ACCE (www.impivacc.org) represented by their coordinators in TRACE, train-the-trainer courses will be organized. For that purpose, we are also very grateful that the European Respiratory Society (ERS, www.ersnet.org) is willing to maintain the GRACE e-learning platform (www.grace-ri.eu), established with the support of both the European Society of Clinical Microbiology and Infectious Diseases Europe (ESCMID, www.escmid.org) and ERS. Since the start, 4 ESF Science Meetings and 2 Steering Committee Meetings have been organized. A 5th ESF Science Meeting and a 3rd Steering Committee meeting will be organized in Nice, France in October 2013. A follow-up audit of GRACE (STRG), a practice based

trial assessing the impact of internet based training packages in communication skills and the use of CRM to modify antibiotic prescribing for LRTI in primary care, was performed to estimate the longer term consequences of the interventions. Over 4000 patients were recruited in 8 networks. In addition, TRACE will facilitate the development of new translational research applications and sustain the expertise in this field.

Together with our partners in 28 EU countries, and our partners in Australia and Hong Kong, we truly hope that TRACE will succeed in sustaining the translational research on antimicrobial resistance and community-acquired infections in Europe and beyond, and in providing compelling evidence for the wisdom of further investment in Networks of Excellence in Europe.

Herman Goossens, Coordinator (Chair)
Samuel Coenen, Manager

* An International Coordination Action granted by the Research Foundation - Flanders (FWO) supports TRACE internationally (TRACE).

Funding

- Bond University Australia | Gold Coast | Queensland | Australia
- Fonds voor Wetenschappelijk Onderzoek - Vlaanderen (FWO) Research Foundation Flanders | Belgium
- University of Antwerp Belgium
- University of Gent Belgium
- Chinese University Hong Kong Division of Family Medicine School of Public Health and Primary Care | China
- University of Copenhagen Denmark
- Suomen Akatemia* Finland
- Finnish Academy of Academy of Finland | Finland
- Finnish Department of Education prior to the start of the OJ-aria (EODES-06) Finland
- Collège Assoctien des Généralistes Enseignants (CGAE) France
- University of Regensburg Germany

- Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) * Netherlands Organisation for Scientific Research | The Netherlands
- University of Amsterdam The Netherlands
- University of Leiden The Netherlands
- University of Utrecht The Netherlands
- Norges Forskningsråd * Research Council of Norway | Norway
- University of Oslo Norway
- University of Tromsø Norway
- Fundacja Centrum Mikrobiologii Klinicznej (CMK) Poland
- Medical University of Budapest Poland
- Medical University of Lodz Poland
- Cardinal National of Covstantin (Institutul din Institutul Superior (CNCSIS)) * National University Research Council, Romania

- Civil Organisation Healthy City Slovakia
- Oostenrijkse Wetenschappelijke Onderzoek (OWO) Slovenia
- Oostenrijkse Wetenschappelijke Onderzoek (OWO) August PI I Sunyer Spain
- Wetenschappelijke Onderzoek (WVO) * Swedish Research Council | Sweden
- Karolinska Institutet Sweden
- Schweizerischer Nationalfonds (SNF) * Swiss National Science Foundation | Switzerland
- Medical Research Council (MRC) * United Kingdom
- University of Southampton United Kingdom
- University of Oxford United Kingdom
- University of Cardiff United Kingdom

* ESF Member Organisation

Steering Committee

- Prof. Herman Goossens (Coordinator)
Herman Goossens, Belgium
- Prof. Lars Engman
Lars Engman, Denmark
- Prof. Heidi Heuvelink
Heidi Heuvelink, Finland
- Dr. Hei Nishitani
Hei Nishitani, France
- Prof. Stella Alsterlund
Stella Alsterlund, Sweden
- Prof. Henry King
Henry King, United Kingdom
- Prof. Thea Steinhilber
Thea Steinhilber, Austria
- Prof. Sjoerd van der Pluijm
Sjoerd van der Pluijm, Netherlands
- Prof. Heiner Bucher
Heiner Bucher, Switzerland
- Prof. Kathrin Mühlemann
Kathrin Mühlemann, Switzerland

Contact info

- Prof. Samuel Coenen
Manager
samuel.coenen@ua.ac.be
- M. Anne Straygen
Administrator TRACE (ESF)
T +31 3 203 23 98
anne.straygen@ua.ac.be
- Dr. Katherine Levens
Administrator TRACE (FWO)
T +31 3 203 23 97
katherine.levens@ua.ac.be
- Science & Infectious Disease Institute (S&IDI/ICTG)
Department of Medical Microbiology
University of Antwerp
Belgium

www.esf.org/trace

Spreading excellence in respiratory tract infections

The effect of web-based training in communication skills and an interactive patient booklet and the use of a CRP point of care test in acute respiratory tract infection (RTI): a multi-national cluster randomised factorial controlled trial.

Paul Little, Beth Stuart, Nick Francis, Sarah Tonkin-Crine, Elaine Douglas, Sibyl Anthierens, Jochen WL Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, Gilly O'Reilly, Alike van der Velden, Adam WA Geraghty, Herman Goossens, Theo Verheij, and Lucy Yardley on behalf of the GRACE consortium. *Lancet* 2013;382:1175-82.

A major 'driver' of antibiotic resistance is prescribing in primary care, and the volume of antibiotic use is rising. Interactive workshops and patient education reduce prescribing, but they rely on highly trained staff at centres of excellence.

246 primary care practices in six European countries were cluster randomised in a factorial design using computer-generated random numbers to four groups: 1) Usual care (control) 2) Internet training for a C reactive protein (CRP) Point of care test (POCT) and demonstration of POCT device 3) Internet training in communication skills and using an interactive patient information booklet 4) Both (CRP/communication).

During a baseline audit (October-December2010), 3742/ 6771(55%) patients with acute lower (LRTIs) and upper RTIs (URTIs) were prescribed antibiotics. Following randomisation 4264 patients were recruited (February-May2011): 80% had LRTI, and 58% of controls were prescribed antibiotics. CRP training reduced prescribing (training 33% vs no training 48%; adjusted risk ratio 0.54, 95% confidence interval 0.42 to 0.69) as did communication training (36% vs 45%; 0.69, 0.54 to 0.87). Combined intervention performed best (risk ratios: CRP 0.53, Communication 0.68, Combined 0.38). Duration of symptoms rated moderately bad was similar with CRP training (median 5 days vs no training 5 days: hazard ratio 0.93;0.83 to 1.04)) and one more day with communication training (6 vs 5 days; 0.83;0.74 to 0.93), but symptom severity was similar, and there were non-significant increases for new or worsening symptoms (CRP training 19% vs no training 18%; communication training 20% vs no training 16%) (Table 1). Reduced antibiotic prescribing was similar for LRTIs and URTIs. There were few hospital admissions (control 2; CRP 10; Communication 6; Combined 12).

The authors demonstrated that internet training to use a CRP POCT, or enhanced communication skills plus interactive patient information booklet, achieved important reductions in antibiotic prescribing for RTIs, and the combined intervention performed best.

Table 1. Effectiveness of CRP and Enhanced Communication skills training in reducing antibiotic prescribing (factorial analysis: risk ratios with 95% confidence intervals; p-value)

		No CRP training	CRP training	No communication training	Communication training
Antibiotics Prescribed	Crude percentage	48% (984/2040)	33% (734/2224)	45% (876/1932)	36% (842/2332)
	¹ Basic Risk ratio	1.00	0.58 (0.48,0.70; p<0.001)	1.00	0.76 (0.63,0.89; p <0.001)
	² Adjusted Risk ratio	1.00	0.54 (0.42, 0.69; p <0.001)	1.00	0.69 (0.54, 0.87; p< 0.001)

¹Basic Risk ratio: model adjusts only for baseline prescribing and clustering by GP and practice.

²Adjusted' risk ratio: more fully adjust model additionally controlled for: Age, smoking, gender, major cardiovascular or respiratory comorbidity, baseline symptoms crepitations, wheeze, pulse>100, temp >37.8, Respiratory rate, BP, GP rating of severity, and prior duration cough.

Strategies to promote prudent antibiotic use: exploring the views of professionals who develop and implement guidelines and interventions.

Sarah Tonkin-Crine, Lucy Yardley, Samuel Coenen, Patricia Fernandez-Vandellos, Jaroslaw Krawczyk, Pia Touboul, Theo Verheij, Paul Little. *Fam Pract* 2013;30:88-95.

A variety of interventions have been developed to promote prudent antibiotic use, especially for respiratory tract infections (RTIs); however, it is not yet clear which are most acceptable and feasible for implementation across a wide range of contexts. This study elicited the views of experts, professionals who develop and implement guidelines and interventions, from five countries (Table 2), on the development of RTI guidelines and interventions for implementing them.

The aim was to determine whether there are common features of interventions which experts consider useful in changing health professionals' behaviour, or whether there are important contextual differences in views.

Fifty semi-structured interviews explored experts' views and experiences of strategies across five countries. Interviews were carried out in person or over the phone, transcribed verbatim and translated into English, if not already in English, for analysis.

Themes were remarkably consistent across the countries, and these could be summarized as five sets of recommendations: guidelines should be developed by health care professionals to better fit GPs' needs; address GP concerns about recommendations and explain the need for guidelines; design flexible interventions to increase feasibility across primary care practice; provide interventions which engage GPs; and provide consistent messages about antibiotic use for patients, professionals and the public.

In conclusion, key features need to be addressed when developing future guidelines and interventions in order to improve their implementation. Consistency in experts' views across countries indicates the potential for the development of interventions which could be implemented on a multinational scale with widespread support from key opinion leaders.

Table 2. The number of experts who report having had experience in developing or implementing five types of strategies across the five countries.

	Belgium	France	Poland	Spain	UK	Total
Guideline Development	7	8	6	10	5	36 (71%)
Educational Meetings	7	6	9	3	6	31 (61%)
Public Campaigns	2	2	6	0	0	10 (20%)
Financial Incentives	0	0	1	2	0	3 (6%)
Prescribing Feedback	3	0	0	0	0	3 (6%)

*Groups are not exclusive as some experts report having had experience in more than one type of strategy.

Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study.

Saskia van Vugt, Lidewij Broekhuizen, Christine Lammens, Nicolaas PA Zuithoff, Pim de Jong, Samuel Coenen, Margareta Ieven, Christopher C Butler, Herman Goossens, Paul Little, Theo Verheij. *BMJ* 2013;346:f2450.

To quantify the diagnostic accuracy of selected inflammatory markers in addition to symptoms and signs for predicting pneumonia and to derive a diagnostic tool a diagnostic study was performed between 2007 and 2010 in primary care centres in 12 European countries. Adults presenting with acute cough were enrolled.

Participants had their history taken, underwent physical examination and measurement of C reactive protein (CRP) and procalcitonin in venous blood on the day they first consulted, and underwent chest radiography within seven days. Pneumonia was determined by radiologists, who were blind to all other information when they judged chest radiographs.

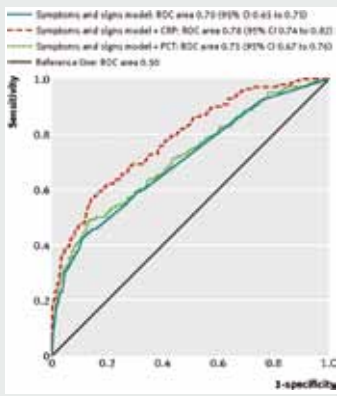


Figure 2. ROC curves of symptoms and signs and added value CRP and procalcitonin (continuous results).

Linear predictors for estimated risk of pneumonia: symptoms and signs = $1/(1+\exp(-3.984+0.446\times\text{breathlessness}+0.698\times\text{absence of runny nose}+0.596\times\text{diminished vesicular breathing}+1.404\times\text{crackles}+0.961\times\text{tachycardia}+0.980\times\text{temperature} >37.8^\circ\text{C}))$; symptoms signs and CRP = $1/(1+\exp(-4.270+0.446\times\text{breathlessness}+0.698\times\text{absence of runny nose}+0.596\times\text{diminished vesicular breathing}+1.404\times\text{crackles}+0.961\times\text{tachycardia}+0.980\times\text{temperature} >37.8^\circ\text{C}+0.130\times(\text{CRP}/10)))$; symptoms signs and PCT = $1/(1+\exp(-4.023+0.446\times\text{breathlessness}+0.698\times\text{absence of runny nose}+0.596\times\text{diminished vesicular breathing}+1.404\times\text{crackles}+0.961\times\text{tachycardia}+0.980\times\text{temperature} >37.8+0.160\times(\text{PCT}\times 10)))$.

Of 3106 eligible patients, 286 were excluded because of missing or inadequate chest radiographs, leaving 2820 patients (mean age 50, 40% men) of whom 140 (5%) had pneumonia. Re-assessment of a subset of 1675 chest radiographs showed agreement in 94% (κ 0.45, 95% confidence interval 0.36 to 0.54). Six published «symptoms and signs models» varied in their discrimination (area under receiver operating characteristics curve (ROC) ranged from 0.55 (95% confidence interval 0.50 to 0.61) to 0.71 (0.66 to 0.76)). The optimal combination of clinical prediction items derived from our patients included absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever, with an ROC area of 0.70 (0.65 to 0.75) (Fig. 2). Addition of CRP at the optimal cut off of >30 mg/L increased the ROC area to 0.77 (0.73 to 0.81) and improved the diagnostic classification (net reclassification improvement 28%). In the 1556 patients classified according to symptoms, signs, and CRP >30 mg/L as «low risk» (<2.5%) for pneumonia, the prevalence of pneumonia was 2%. In the 132 patients classified as «high risk» (>20%), the prevalence of pneumonia was 31%. The positive likelihood ratio of low, intermediate, and high risk for pneumonia was 0.4, 1.2, and 8.6 respectively. Measurement of procalcitonin added no relevant additional diagnostic information. A simplified diagnostic score based on symptoms, signs, and CRP >30 mg/L resulted in proportions of pneumonia of 0.7%, 3.8%, and 18.2% in the low, intermediate, and high risk group respectively.

In conclusion, a clinical rule based on symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough performed best in patients with mild or severe clinical presentation. Addition of CRP concentration at the optimal cut off of >30 mg/L improved diagnostic information, but measurement of procalcitonin concentration did not add clinically relevant information in this group.

Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study.

Fiona Wood, Carys Phillips, Lucy Brookes-Howell, KerENZA Hood, Theo Verheij, Samuel Coenen, Paul Little, Hasse Melbye, Maciek Godycki-Cwirko, Kristin Jakobson, Herman Goossens, Christopher C Butler. *Antimicrob Chemother* 2013;68:237-43.

The objective of this study was to explore and compare primary care clinicians' perceptions of antibiotic resistance in relation to the management of community-acquired lower respiratory tract infection (LRTI) in contrasting European settings.

A qualitative interview study with 80 primary care clinicians in nine European countries was performed (Table 3). Data were subjected to a five-stage analytical framework approach (familiarization; developing a thematic framework from the interview questions and the themes emerging from the data; indexing; charting; and mapping to search for interpretations in the data). Preliminary analysis reports were sent to all network facilitators for validation.

Most clinicians stated that antibiotic resistance was not a problem in their practice. Some recommended enhanced feedback about local resistance rates. Northern European respondents generally favoured using the narrowest-spectrum agent, motivated by containing resistance, whereas southern/eastern European respondents were more motivated by maximizing the potential of a rapid treatment effect and so justified empirical use of broad-spectrum antibiotics. Antibiotic treatment failure was ascribed largely to viral aetiology rather than resistant bacteria. Clinicians generally agreed that resistance will become more serious without enhanced antibiotic stewardship or new drug discovery.

If current rates of antibiotic resistance are likely to result in important treatment failures, then provision of local resistance data is likely to enhance clinicians' sense of importance of the issue. Interventions to enhance the quality of antibiotic prescribing in primary care should address perceptions, particularly in the south and east of Europe, that possible advantages to patients from antibiotic treatment in general, and from newer broad-spectrum compared with narrow-spectrum agents, outweigh disadvantages to patients and society from associated effects on antibiotic resistance.

Network	Number of clinicians interviewed
Antwerp (Belgium)	10
Balatonfüred (Hungary)	10
Barcelona (Spain)	10
Cardiff (Wales)	8
Lodz (Poland)	10
Milan (Italy)	9
Southampton (England)	6
Tromsø (Norway)	7
Utrecht (The Netherlands)	10

Table 3. Number of clinicians interviewed in each network.

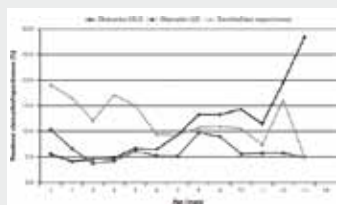


Figure 3. Prevalence of airway obstruction and bronchodilator responsiveness in patients consulting for acute cough, by diagnostic definition and age-group.

ERS = European Respiratory Society; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal.

Note: obstruction GOLD = according to the GOLD definition: FEV₁:FVC less than 0.70. Obstruction LLN = according to ERS: LLN of FEV₁:FVC ratio for male patients: $-0.18 \times \text{age} + 87.21 - (1.64 \times 7.17)$; for female patients: $-0.19 \times \text{age} + 89.10 - (1.64 \times 6.51)$.

Airway obstruction and bronchodilator responsiveness in adults presenting with acute cough.

Saskia van Vugt, Lidewij Broekhuizen, Nicolaas Zuithoff, Pim de Jong, Christopher Butler, Kerenza Hood, Samuel Coenen, Herman Goossens, Paul Little, Jordi Almirall, Francesco Blasi, Slawomir Chlabicz, Mel Davies, Maciek Godycki-Cwirko, Helena Hupkova, Janko Kersnik, Michael Moore, Tom Schaberg, An De Sutter, Antoni Torres, Theo Verheij on behalf of the GRACE Project Group. *Ann Fam Med* 2012; 10:523-9.

The objective of this paper was to determine the prevalence of airway obstruction and bronchodilator responsiveness in adults consulting for acute cough in primary care.

Family physicians recruited 3,105 adult patients with acute cough (28 days or shorter) attending primary care practices in 12 European countries. After exclusion of patients with preexisting physician-diagnosed asthma or chronic obstructive pulmonary disease (COPD), a complete case analysis of spirometry results ($n = 1,947$) 28 to 35 days after inclusion was undertaken. Bronchodilator responsiveness was diagnosed if there were recurrent complaints of wheezing, cough, or dyspnea and an increase of the forced expiratory volume in 1 second (FEV₁) of 12% or more after bronchodilation. Airway obstruction was diagnosed according to 2 thresholds for the (postbronchodilator) ratio of FEV₁ to forced vital capacity (FEV₁:FVC): less than 0.7 and less than the lower limit of normal.

There were 240 participants who showed bronchodilator responsiveness (12%), 193 (10%) had a FEV₁/FVC ratio of less than 0.7, and 126 (6%) had a ratio of less than the lower limit of normal. Spearman's correlation between the 2 definitions of obstruction was 0.71 ($P < .001$), with discordance most pronounced among those younger than 30 years and in older participants.

The data show that both bronchodilator responsiveness and persistent airway obstruction are common in adults without established asthma or COPD who consult for acute cough in primary care, which suggests a high risk of undiagnosed asthma and COPD. Different accepted methods to define airway obstruction detected different numbers of patients, especially at the extremes of age. As both conditions benefit from appropriate and timely interventions, clinicians should be aware and responsive to potential underdiagnosis.

Delayed antibiotic prescribing and associated antibiotic consumption in adults with acute cough.

Nick Francis, David Gillespie, Jacqui Nuttall, Kerenza Hood, Paul Little, Theo Verheij, Herman Goossens, Samuel Coenen, Christopher C Butler. *Gen Pract* 2012; e639-46.

Delayed antibiotic prescribing is promoted as a strategy to reduce antibiotic consumption, but its use and its effect on antibiotic consumption in routine care is poorly described. This study aims to quantify delayed antibiotic prescribing in adults presenting in primary care with acute cough/lower respiratory tract infection (LRTI), duration of advised delay, consumption of delayed antibiotics, and factors associated with consumption.

In a prospective observational cohort in general practices in 14 primary care networks in 13 European countries GPs recorded clinical features and antibiotic prescribing for adults presenting with an acute infective illness with cough as the dominant symptom. Patients recorded their consumption of antibiotics from any source during the 28-day follow up.

Two hundred and ten (6.3%) of 3368 patients with usable consultation data were prescribed delayed antibiotics. The median recommended delay period was 3 days. Seventy-five (44.4%) of the 169 with consumption data consumed the antibiotic course and a further 18 (10.7%) took another antibiotic during the study period. 50 (29.6%) started their delayed course on the day of prescription. Clinician diagnosis of upper respiratory tract/viral infection and clinician's perception of patient's wanting antibiotics were associated with less consumption of the delayed prescription. Patient's wanting antibiotics was associated with greater consumption.

In conclusion, delayed antibiotic prescribing was used infrequently for adults presenting in general practice with acute cough/LRTI. When used, the effect on antibiotic consumption was less than found in most trials. There are opportunities for standardising the intervention and promoting wider uptake.

No novel coronaviruses identified in a large collection of human nasopharyngeal specimens using family-wide CODEHOP-based primers.

Kalina Zlateva, Frank E Coenjaerts, Kelly M. Crusio, Christine Lammens, Frank Leus, Marco Viveen, Margareta Ieven, Willy J Spaan, Eric C Claas, Alexander E Gorbalenya. *Arch Virol* 2013;158:251-5.

Novel viruses might be responsible for numerous disease cases with unknown etiology. In this study, we screened 1800 nasopharyngeal samples from adult outpatients with respiratory disease symptoms and healthy individuals. We employed a reverse transcription (RT)-PCR assay and CODEHOP-based primers (CT12-mCODEHOP) previously developed to recognize known and unknown corona- and toroviruses. The CT12-mCODEHOP assay detected 42.0 % (29/69) of samples positive for human coronaviruses (HCoV), including HCoV-229E (1/16), HCoV-NL63 (9/17), and HCoV-OC43 (19/36), and additionally HCoV-HKU1 (3), which was not targeted by the diagnostic real-time PCR assays (Table 5). No other coronaviruses were identified in the analyzed samples.

Table 5. Detection of human coronaviruses using the CT12-mCODEHOP one-step RT-PCR assay in nasopharyngeal swabs that were positive for coronavirus by real-time PCR^a

Coronavirus	N ^b	Detected		Not detected	
		N (%)	Ct IQM (IQR) ^c	N (%)	Ct IQM (IQR) ^c
HCoV-229E	16	1 (6.7 %)	21.14	15 (93.7 %)	28.28 (22.79-31.87)
HCoV-NL63	17	9 (53 %)	23.63 (22.0-27.52)	8 (47 %)	28.88 (27.10-34.28)
HCoV-OC43	36	19 (52.8 %)	26.21 (22.44-27.56)	17 (47.2 %)	33.04 (30.68-34.85)
All HCoVs	69	29 (42.0 %)	25.32 (22.03-27.52)	40 (58.0 %)	30.68 (27.75-34.51)

^aHCoVs were initially detected using a multiplex coronavirus real-time RT-PCR and then typed by monoplex real-time PCR assays. Cycle threshold number (Ct) values obtained by both methods were similar, and the monoplex-based results are presented in the table

^bTotal number of HCoV-positives

^cIQM, interquartile median and IQR, interquartile range, for Ct values

The first complete genome sequences of clinical isolates of human coronavirus 229E.

Seyed M Farsani, Ronald Dijkman, Maarten F Jebbink, Herman Goossens, Margareta Ieven, Martin Deijls, Richard Molenkamp, Lia van der Hoek. *Virus Genes* 2012;45:433-9.

Human coronavirus 229E has been identified in the mid-1960s, yet still only one full-genome sequence is available. This full-length sequence has been determined from the cDNA-clone Inf-1 that is based on the lab-adapted strain VR-740. Lab-adaptation might have resulted in genomic changes, due to insufficient pressure to maintain gene integrity of non-essential genes. Farsani et al. present here the first full-length genome sequence of two clinical isolates. Each encoded gene was compared to Inf-1. In general, little sequence changes were noted, most could be attributed to genetic drift, since the clinical isolates originate from 2009 to 2010 and VR740 from 1962. Hot spots of substitutions were situated in the S1 region of the Spike, the nucleocapsid gene, and the non-structural protein 3 gene, whereas several deletions were detected in the 3'UTR. The phylogenetic analysis is presented in Fig 4. Most notable was the difference in genome organization: instead of an ORF4A and ORF4B, an intact ORF4 was present in clinical isolates.

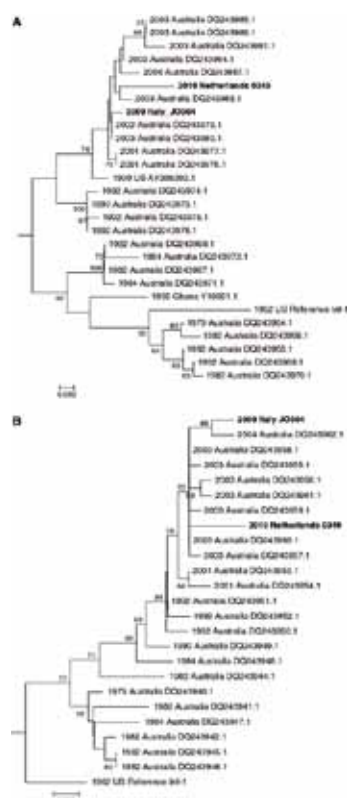


Figure 4. Phylogenetic analysis of the a spike and b nucleocapsid genes of the HCoV-229E clinical isolates, Inf-1 and those available in GenBank (accession numbers, year, and country of collection are indicated)



Third Steering Committee Meeting and sixth ESF Science Meeting

On October 4th, the third TRACE Steering Committee Meeting was held in Nice, France. This meeting preceded the ESF Science Meeting "General Practice Respiratory Infections Network Meeting 2013" held at the same venue on 4 and 5 October. Both meetings were very well attended.

The Steering Committee welcomed two new members and the new Science Officer (see p.2). TRACE involvement in PREPARE (see p.1), in particular the primary care studies, was a major topic during the meeting. It was agreed that the primary care networks included in the Description of Work of PREPARE will be invited to join TRACE. This would mean an expansion of TRACE to Greece, Hungary, Ireland, Lithuania, Portugal, and Romania, and include primary care networks in Spain (Mataro and SemFYC) and Sweden (Jonköping). In the context of PREPARE COMBACTE was presented. COMBACTE forms part of the New Drugs for Bad Bugs (ND4BB) initiative, the Innovative Medicines Initiative (IMI)'s wider programme to tackle antimicrobial resistance. COMBACTE set up a dynamic hospital network of currently over 600 hospitals in 35 European countries to match the TRACE primary care network including over 600 practice in 19 European countries. In addition, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMRI) and its focus on antimicrobial resistance in hospitals was discussed.

During the GRIN Meeting 2013, next to keynote speaker Clodna McNulty, 34 primary care researcher from 11 different European countries presented their work in three sessions on diagnostics and aetiology, antibiotic use, and treatment effect on disease course, respectively. These presentations included many GRACE results, and were mixed with lively discussions and calls for collaboration during the sessions and the social programme. The next Steering Committee Meeting as well as the next GRIN Meeting will be held in Antwerp, Belgium, on 3 October 2014 and 3-4 October 2014, respectively. Antwerp is not Nice, but it definitely very nice!

Samuel Coenen



Colophon

Design

Natacha Hoevenaegel
Nieuwe Media Dienst
Universiteit Antwerpen

Editorial team

Samuel Coenen
Katherine Loens

Contributors

Chris Butler
Samuel Coenen
Nick Francis
Herman Goossens
Alexander Gorbalenya
Paul Little
Katherine Loens
Lia van der Hoek
Saskia van Vugt
Theo Verheij

TRACE project leader

Herman Goossens
University of Antwerp - CDE
Laboratory of Microbiology
Universiteitsplein 1
2610 Antwerp
Belgium
www.esf.org/trace