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

TRACE news

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Editorial

TRACE primary care research networks in PREPARE intervention study

TRACE is involved in the FP7 project PREPARE (Platform foR European Preparedness Against (Re-)emerging Epidemics), which was kicked-off in February 2014 in Antwerp, Belgium (see TRACE News October 2013 and www.prepare-europe.eu). The overall mission of PREPARE is to establish a European clinical research framework for harmonised, large-scale clinical research studies on infectious diseases enabling a rapid response to any severe infectious disease outbreak, by providing real-time evidence for clinical management of patients and for public health responses. Within PREPARE five research platforms, comprising 11 work packages, will be operative, of which the following deal with clinical research:

- PRACTICE: clinical and regulatory platform for rapid implementation of harmonised, effective, safe and clinically useful patient-oriented research and clinical trials in Europe, enabling an integrated clinical research response to any severe infectious disease outbreak
- PATHOS: platform for rapid deployment of pathogenesis research studies
- PREDICT: platform for research and support on diagnostics for infectious diseases

TRACE will participate in PRACTICE study B: A multi-centre European randomised intervention trial on the (cost)-effectiveness of flu medication and the use of point-of-care tests in children, adults and seniors presenting with influenza-like illness (ILI) in primary care during a period of high influenza incidence.
ALIC^{4}E (Antivirals for influenza Like Illness? An rCt of Clinical and Cost effectiveness in primary CarE) is coordinated by TRACE partners and will be an open, adaptive, randomised trial, which will allow to evaluate established antivirals, as well as to add emerging, promising antivirals during the course of the trial for their (cost) effectiveness in every day primary care. The aim is to include 80 patients from each network in 20 EU countries per flu season (as determined by the national influenza surveillance body). The trial will be run over three consecutive flu seasons and begin with evaluating ILI treatment with oseltamivir, nitazoxanide and defined usual care.
Coordinators and a staff member from each network will be invited for the first ALIC^{4}E coordinator meeting in Oxford 9-10 January 2015, where the scientific background, protocol, logistical requirements, optimised patient inclusion, education of study personnel will be presented and discussed together. For the TRACE networks this will surely be the exciting start of an endeavour matching the challenges of the GRACE studies, providing equally relevant primary care evidence and preparing a unique primary care research infrastructure to rapidly respond to any severe infectious disease outbreak.

Samuel Coenen

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News

TRACE @ ECCMID 2014

A TRACE poster was presented at the European corner of the ECCMID 2014 held in Barcelona from May 10 to May 13. The TRACE leaflet was distributed among the >10.000 participants.

Two posters acknowledging TRACE were presented as well:

1) Are PCR and single IgG measurement in convalescent serum complementary for the diagnosis of an acute *B. pertussis* infection? Presented by Loens K, Huygen K, Verheij T, Teepe J, Lammens C, Goossens H and Ieven M.
2) Evaluation of the new RespiFinder for the detection of respiratory pathogens. Presented by Loens K, Lammens C, Goossens H, Coenjaerts F, Claas E, van Loon A and Ieven M for the GRACE study team.

TRACE @ 2014 NAPCRG Conference

Two abstracts were selected for an oral presentation at the NAPCRG conference held in New York from November 21 to November 25.

1) Teepe J, Broekhuizen BDL, Ieven M, Lammens C, Huygen K, Loens K, Goossens H, Verheij TJM on behalf of the GRACE consortium. Disease course of *Bordetella pertussis* infection in primary care.
2) Teepe J, Broekhuizen BDL, Ieven M, Lammens C, Huygen K, Loens K, Goossens H, Verheij TJM on behalf of the GRACE consortium Detecting *Bordetella pertussis* infection in adults with acute cough.

New TRACE members

Jaana Vuopio of the Department of Medical Microbiology and Immunology at the University of Turku (Finland) agreed to be the new Finnish representative for the Suomen Akatemia, an ESF Member Organisation supporting TRACE. She succeeds Pentti Huovinen who has been nominated and meanwhile has taken on new duties as the Dean of the Medical Faculty at the University of Turku.

GRACE PhD

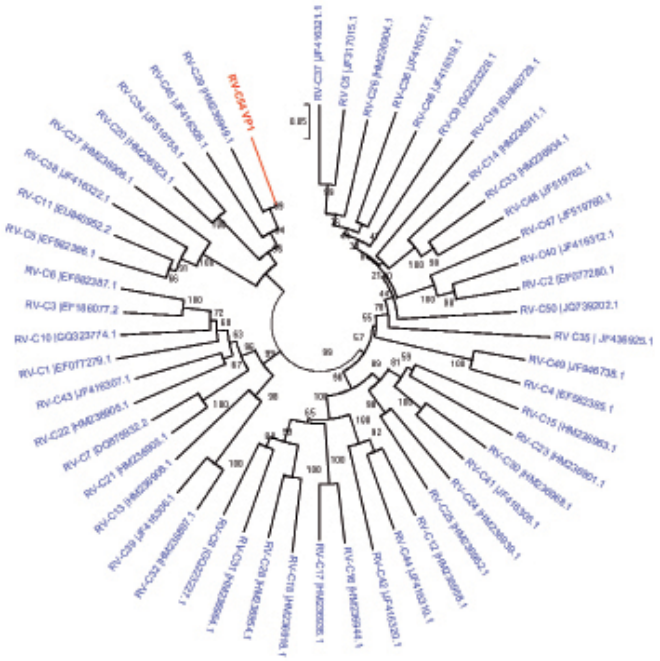
Jazaeri Farsani S, van der Hoek C, Berkhout B. Respiratory viruses and novel methods for virus discovery. Amsterdam: Amsterdam Medical Center - University of Amsterdam; 2014. p. 134.

On October 2014, Seyed Mohammad Jazaeri Farsani, successfully defended his PhD thesis "Respiratory viruses and novel methods for virus discovery".
Viral infections represent the majority of emerging infectious diseases in humans. The etiology of a substantial part remains unknown and it is likely that a fair percentage of these diseases are caused by unknown viruses. Therefore, identification of new viruses and improvement of the methods to discover yet-unknown viruses are important. Nowadays, application of molecular methods such as high throughput sequencing in virus discovery becomes more frequent (e.g. VIDISCA-454). These technologies are able to provide ten thousands or even millions of sequences from a clinical sample, facilitating exploration of new viral agents and virus evolution. However, the determination of clinical relevance of new viral pathogens remains a significant challenge. To this end, virus discovery techniques should be optimized to not only detect new viruses in clinical samples but also provide preliminary data about infectivity and pathogenesis of novel viruses.

In this thesis, two approaches are described to optimize the virus discovery: 1) linkage of VIDISCA-454 to culturing in human airway epithelial cells and 2) antibody capture VIDISCA-454. Both approaches were developed using clinical samples from the GRACE cohort. The first technique uses a universal cell culture system for respiratory viruses, human airway epithelium cell culture, combined with VIDISCA-454 to create a virus discovery tool with the added possibility to provide information about infectiousness and cell tropism of new viruses. The second technique is antibody capture VIDISCA-454 which provides an important first step in the identification of a disease-related virus. Convalescent serum of the patient can be used to concentrate viruses that have elicited an immune response. Thus, this method facilitates virus identification by enrichment of virus-derived material, which was confirmed by detection of a novel virus, the 54th type of rhinovirus C in one of the patient from the GRACE cohort.

This thesis is available by sending an email to s.m.jazaerifarsani@amc.uva.nl.

Lia van der Hoek



Phylogenetic tree based on nucleotide sequences of the VP1 gene.
HRV-C54 is indicated in red

Spreading excellence in respiratory tract infections

Isolation and characterization of current human coronavirus strains in primary human epithelial cell cultures reveal differences in target cell tropism.

Ronald Dijkman, Maarten F Jebbink, Sylvie M Koekkoek, Martin Deijs, Hulda R Jónsdóttir, Richard Molenkamp, Margareta Ieven, Herman Goossens, Volker Thiel, Lia van der Hoek. J Virol 2013;87:6081-90.

The human airway epithelium (HAE) represents the entry port of many human respiratory viruses, including human coronaviruses (HCoVs). Nowadays, four HCoVs, HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63, are known to be circulating worldwide, causing upper and lower respiratory tract infections in nonhospitalized and hospitalized children. Studies of the fundamental aspects of these HCoV infections at the primary entry port, such as cell tropism, are seriously hampered by the lack of a universal culture system or suitable animal models. To expand the knowledge on fundamental virus-host interactions for all four HCoVs at the site of primary infection, we used pseudostratified HAE cell cultures to isolate and characterize representative clinical HCoV strains directly from nasopharyngeal material. Ten contemporary isolates were obtained, representing HCoV-229E (n = 1), HCoV-NL63 (n = 1), HCoV-HKU1 (n = 4), and HCoV-OC43 (n = 4). For each strain, we analyzed the replication kinetics and progeny virus release on HAE cell cultures derived from different donors. Surprisingly, by visualizing HCoV infection by confocal microscopy, we observed that HCoV-229E employs a target cell tropism for nonciliated cells, whereas HCoV-OC43, HCoV-HKU1, and HCoV-NL63 all infect ciliated cells (Figure 1). Collectively, the data demonstrate that HAE cell cultures, which morphologically and functionally resemble human airways in vivo, represent a robust universal culture system for isolating and comparing all contemporary HCoV strains.

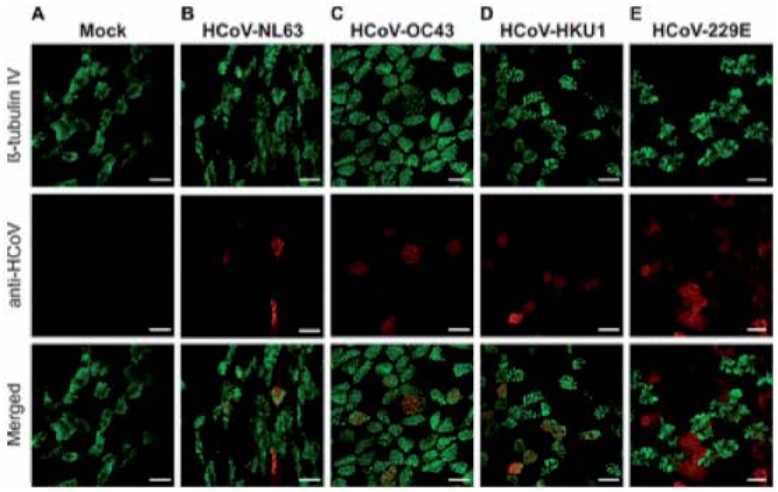


Figure 1. Cell tropisms of representative clinical HCoV isolates. Human airway epithelial cell cultures were fixed at 120 hpi, followed by double immunostaining with monoclonal anti-ß-tubulin IV to detect ciliated cells (green) and human IVIg to detect HCoV proteins (red), and were then examined by confocal microscopy. Magnification, ×40. Representative images at 120 hpi are presented for a control culture (A) and for HCoV-NL63 (B)-, HCoV-OC43 (C)-, HCoV-HKU1 (D)-, and HCoV-229E (E)-inoculated cultures. An overlay image was generated to determine the cell tropism of each HCoV isolate. Bars, 20 µm.

Metagenomic analysis of a sample from a patient with respiratory tract infection reveals the presence of a γ-papillomavirus.

Marta Canuti, Martin Deijs, Seyed M Jazaeri Farsani, Melle Holwerda, Maarten F Jebbink, Michel de Vries, Saskia van Vugt, Curt Brugman, Theo Verheij, Christine Lammens, Herman Goossens, Katherine Loens, Margareta Ieven, and Lia van der Hoek. Front Microbiol 2014 8;5:347.

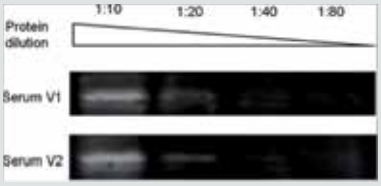


Figure 2. No increase in antibody levels directed to γ-papillomavirus A2619. Visit 1 (V1) and Visit 2 (V2) sera were diluted 1:600 and incubated on Western blot containing a dilution series of L1 protein.

Previously unknown or unexpected pathogens may be responsible for that proportion of respiratory diseases in which a causative agent cannot be identified. The application of broad-spectrum, sequence independent virus discovery techniques may be useful to reduce this proportion and widen our knowledge about respiratory pathogens. Thanks to the availability of high-throughput sequencing (HTS) technology, it became today possible to detect viruses which are present at a very low load, but the clinical relevance of those viruses must be investigated. In this study we used VIDISCA-454, a restriction enzyme based virus discovery method that utilizes Roche 454 HTS system, on a nasal swab collected from a subject with respiratory complaints. A γ-papillomavirus was detected (complete genome: 7142 bp) and its role in disease was investigated. Respiratory samples collected both during the acute phase of the illness and 2 weeks after full recovery contained the virus. The patient presented antibodies directed against the virus but there was no difference between IgG levels in blood samples collected during the acute phase and 2 weeks after full recovery (Figure 2). We therefore concluded that the detected γ-papillomavirus is unlikely to be the causative agent of the respiratory complaints and its presence in the nose of the patient is not related to the disease. Although HTS based virus discovery techniques proved their great potential as a tool to clarify the etiology of some infectious diseases, the obtained information must be subjected to cautious interpretations. This study underlines the crucial importance of performing careful investigations on viruses identified when applying sensitive virus discovery techniques, since the mere identification of a virus and its presence in a clinical sample are not satisfactory proofs to establish a causative link with a disease.

Medication use in European primary care patients with lower respiratory tract infection: an observational study.

Marleen Hamoen, Berna D Broekhuizen, Paul Little, Hasse Melbye, Samuel Coenen, Herman Goossens, Christopher C Butler, Nick A Francis, Theo J Verheij; GRACE clinical study group. Br J Gen Pract 2014;64:e81-91.

It is largely unknown what medication is used by patients with lower respiratory tract infection (LRTI). The aim of this study is to describe the use of self-medication and prescribed medication in adults presenting with LRTI in different European countries, and to relate self-medication to patient characteristics. An observational study in 16 primary care networks in 12 European countries was set-up. A total of 2530 adult patients presenting with LRTI in 12 European countries filled in a diary on any medication used before and after a primary care consultation. Patient characteristics related to self-medication were determined by univariable and multivariable logistic regression analysis.
The frequency and types of medication used differed greatly between European countries. Overall, 55.4% self-medicated before consultation, and 21.5% after consultation, most frequently with paracetamol, antitussives, and mucolytics. Females, non-smokers, and patients with more severe symptoms used more self-medication. Patients who were not prescribed medication during the consultation self-medicated more often afterwards. Self-medication with antibiotics was relatively rare.
In conclusion, a considerable amount of medication, often with no proven efficacy, was used by adults presenting with LRTI in primary care. There were large differences between European countries. These findings should help develop patient information resources, international guidelines, and international legislation concerning the availability of over-the-counter medication, and can also support interventions against unwarranted variations in care. In addition, further research on the effects of symptomatic medication is needed.

IFITM3 and susceptibility to respiratory viral infections in the community.

Tara C Mills, Anna Rautanen, Katherine S Elliott, Tom Parks, Vivek Naranbhai, Margareta M Ieven, Christopher C Butler , Paul Little, Theo Verheij, Chris S Garrard, Charles Hinds, Herman Goossens, Steve Chapman, and Adrian V Hill. J Infect Dis 2014;209:1028-31.

Interferon-inducible transmembrane proteins 1, 2, and 3 (IFITM 1,2, and 3) are viral restriction factors that mediate cellular resistance to several viruses. We have genotyped a possible splice-site altering single-nucleotide polymorphism (rs12252) in the IFITM3 gene in 34 patients with H1N1 influenza and severe pneumonia, and >5000 individuals comprising patients with community-acquired mild lower respiratory tract infection and matched controls of Caucasian ancestry. We found evidence of an association between rs12252 rare allele homozygotes and susceptibility to mild influenza (in patients attending primary care) but could not confirm a previously reported association between this single-nucleotide polymorphism and susceptibility to severe H1N1 infection (Table 1).

Table 1. Association Results for *IFITM3* SNP rs12252[a]

Association	Patients by Study and Infection						
	GRACE Controls (n = 2623)	Everitt et al [1] Influenza (n = 53)	GAinS H1N1 (n = 34)	GAinS H1N1 and Everitt et al [3] Influenza (n = 87)	GRACE Mild Viral Infection (n = 1248)	GRACE Mild Influenza (n = 259)	GRACE Noninfluenza Viral Infection (n = 989)
HWE P value	>.99	.000048	>.99	.0047	.007	.12	.0248
Genotype, No. (%)							
TT	2417 (92.1)	46 (86.8)	31 (91.2)	77 (88.5)	1160 (92.9)	235 (90.7)	925 (93.5)
CT	202 (7.7)	4 (7.4)	3 (8.8)	7 (8.0)	82 (6.6)	22 (8.5)	60 (6.1)
CC	4 (0.15)	3 (5.6)	0	3 (3.4)	6 (0.48)	2 (0.77)	4 (0.4)
Allelic P value	…	0.011[b]	0.753	0.032[b]	0.764	0.154	0.264
Allelic OR	…	2.498 (1.284–4.861)	1.107 (0.345–3.551)	1.936 (1.082–3.464)	0.960 (0.750–1.229)	1.358 (0.892–2.07)	0.8529 (0.6452–1.127)
Recessive model P value	…	2.4×10^{-4}[b]	>.99	0.001[b]	0.049[b]	0.025[b]	0.150
Recessive model OR	…	39.29 (8.567–180.137)	NA	23.38 (5.152–106.132)	3.59 (1.008–12.79)	7.126 (1.283–39.58)	2.778 (0.6901–11.19)

Abbreviations: GAinS, Genomic Advances in Sepsis; GRACE, Genomics to combat Resistance against Antibiotics in Community acquired LRTI in Europe; HWE, Hardy-Weinberg equilibrium; IFITM3, interferon-inducible transmembrane protein 3; NA, not applicable; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] All analyses included 2623 Caucasian European controls from GRACE. Two-tailed Fisher's exact test was used for the H1N1 analyses (SPSS software, version 18). GRACE patients and controls from across Europe were analyzed using logistic regression in PLINK software with country as a covariate. The HWE *P* values were calculated using PLINK software.

[b] $P < .05$

Variation in family physicians' recording of auscultation abnormalities in patients with acute cough is not explained by case mix. A study from 12 European networks.

Nick Francis, Hasse Melbye, Mark Kelly, Jochen Cals, Rogier Hopstaken, Samuel Coenen, Chris C Butler. Eur J Gen Pract 2013;19:77-84.

Since conflicting data on the diagnostic and prognostic value of auscultation abnormalities may be partly explained by inconsistent use of terminology, the use of chest auscultation abnormality terms for patients presenting with acute cough across Europe by general practitioners were described. Moreover, the influence of geographic location and case mix on use of these terms was explored.

Clinicians recorded whether 'diminished vesicular breathing', 'wheezes', 'crackles' and 'rhonchi' were present in an observational study of adults with acute cough in 13 networks in 12 European countries. The authors describe the use of these terms overall and by network, and used multilevel logistic regression to explore variation by network, controlling for patients' gender, age, comorbidities, smoking status and symptoms.

2345 patients were included in this study. Wheeze was the auscultation abnormality most frequently recorded (20.6% overall) with wide variation by network (range: 8.3-30.8%) (Figure 3). There was similar variation for other auscultation abnormalities. After controlling for patient characteristics, network was a significant predictor of auscultation abnormalities with odds ratios for location effects ranging from 0.37 to 4.46 for any recorded auscultation abnormality, and from 0.25 to 3.14 for rhonchi.

This study shows important variation in recording chest auscultation abnormalities by general practitioners across Europe, which cannot be explained by differences in patient characteristics. There is a need and opportunity for standardization in the detection and classification of lung sounds.

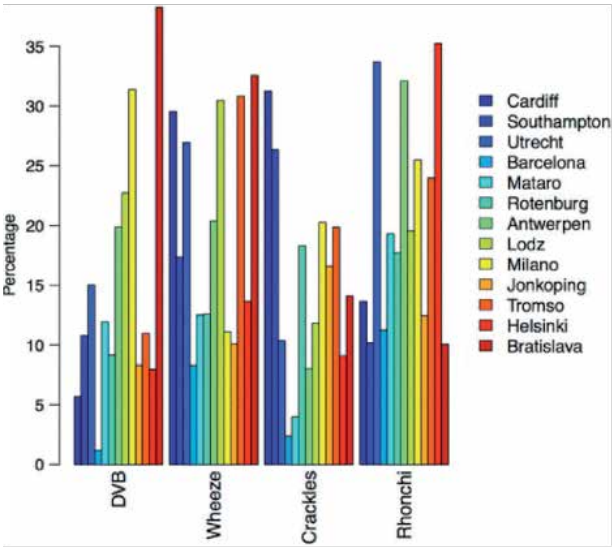


Figure 3. Proportion of patients in each network with each of four auscultation abnormalities. DVB: diminished vesicular breating.

Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography.

Saskia F van Vugt, Theo J Verheij, Pim A de Jong, Christopher C Butler, Kerenza Hood, Samuel Coenen, Herman Goossens, Paul Little, Berna D Broekhuizen for the GRACE Project Group. Eur Respir J 2013;42:1076-82.

Pneumonia is often diagnosed and treated empirically. We set out to determine the diagnostic accuracy of clinical judgment based on signs and symptoms to detect radiographic pneumonia in patients presenting with acute cough in primary care. In 2810 European patients with acute cough, general practitioners (GPs) recorded whether they considered pneumonia to be present ("yes" or "no") immediately after history and physical examination.

Chest radiography was performed within 1 week by local radiologists blind to other patient characteristics. 140 patients had radiographic pneumonia (5%), of whom 41 (29%) had been diagnosed as such (Table 2). 31 (1%) patients had a clinical diagnosis that was not confirmed by radiography (n=2670). In clinically suspected pneumonia (n=72), 57% of subjects were subsequently diagnosed with radiographic pneumonia. Negative predictive value (NPV), sensitivity and specificity of GPs' clinical judgment were 96%, 29% and 99%, respectively. Compared to patients with a clinical diagnosis of pneumonia, less severe symptoms were found in radiographic pneumonia cases not suspected clinically ($p<0.05$).

The predictive values of GPs' clinical judgment, particularly the high NPVs, are helpful in routine care. Nonetheless, the majority of diagnoses of radiographic pneumonias was not suspected on clinical grounds. There is a need to further support the detection of clinically relevant pneumonia in primary care.

Table 2. The general practitioners' (GPs') clinical judgment of pneumonia compared to chest radiography

GPs' judgment	**Chest radiography**		
	Pneumonia present	**Pneumonia absent**	**Total**
Including all countries			
Pneumonia present	41	31	72
Pneumonia absent	99	2639	2738
Total	140	2670	2810
Without including low-prevalence countries			
Pneumonia present	40	28	68
Pneumonia absent	94	1992	2086
Total	134	2020	2154

Data are presented as n.

Incidental findings on chest radiographs in adult primary care patients with acute cough: a twelve-country study.

Saskia van Vugt, Lidewij Broekhuizen, Nicolaas Zuithoff, Pim de Jong, Christopher Butler, Kerenza Hood, Samuel Coenen, Herman Goossens, Paul Little, Jordy Almirall, Francesco Blasi, Slawomir Chlabicz, Melanie Davies, Maciek Godycki-Cwirko, Helena Hupkova, Janko Kersnik, Arthur Mierzcki, Sigvard Mölstad, Michael Moore, Tom Schaberg, An De Sutter, Antoni Torres, Pia Touboul, Theo Verheij on behalf of the GRACE Project Group. Ann Fam Med 2012;10:510-5.

Imaging may produce unexpected or incidental findings with consequences for patients and ordering of future investigations. Chest radiography in patients with acute cough is among the most common reasons for imaging in primary care, but data on associated incidental findings are lacking. This study was set up to describe the type and prevalence of incidental chest radiography findings in primary care patients with acute cough.

The authors report on data from a cross-sectional study in 16 European primary care networks on 3,105 patients with acute cough, all of whom were undergoing chest radiography as part of a research study workup. Apart from assessment for specified signs of pneumonia and acute bronchitis, local radiologists were asked to evaluate any additional finding on the radiographs. For the 2,823 participants with good-quality chest radiographs, these findings were categorized according to clinical relevance based on previous research evidence and analyzed for type and prevalence by network, sex, age, and smoking status.

Incidental findings were reported in 19% of all participants, and ranged from 0% to 25% by primary care network, with the network being an independent contributor (P <.001) (Table 3). Of all participants 3% had clinically relevant incidental findings. Suspected nodules and shadows were reported in 1.8%. Incidental findings were more common is older participants and smokers (P <. 001).

Based on the reported results, it could be concluded that clinically relevant incidental findings on chest radiographs in primary care adult patients with acute cough are uncommon, and prevalence varies by setting.

Table 3. Most frequently reported (potentially) relevant incidental findings in primary care patients with acute cough per sex, age-group, and smoking behavior.

Incidental Finding	Female N=1692 No. (%)	Male N=1131 No. (%)	P Value[a]	≤ 50y N=1388 No. (%)	> 50y N=1435 No. (%)	P Value[a]	Never smoked N=1295 No. (%)	Former or current smoker N=1523 No. (%)	P Value[a]
Any incidental finding	274 (16.2)	250 (22.1)	< 0.001	123 (8.9)	401 (27.9)	< 0.001	207 (16.0)	284 (18.6)	0.044
Suspected nodules, density, or shadow	32 (1.9)	19 (1.7)	0.68	16 (1.2)	35 (2.4)	0.010	24 (1.8)	23 (1.5)	0.27
Hilar/mediastinal enlargement	6 (0.4)	21 (1.9)	< 0.001	12 (0.9)	15 (1.0)	0.62	10 (0.8)	21 (1.3)	0.012
Cardiomegaly or pulmonary congestion	62 (3.7)	38 (3.4)	0.67	17 (1.2)	83 (5.8)	< 0.001	46 (3.0)	48 (3.2)	0.60
Signs of COPD and asthma	61 (3.6)	84 (7.4)	< 0.001	30 (2.2)	115 (8.0)	< 0.001	42 (3.2)	91 (6.0)	<0.001

COPD: chronic obstructive pulmonary disease

[a] Computed using x2 tests. Values considered significant if P<.05.

Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups.

Michael Moore, Beth Stuart, Samuel Coenen, Christopher C Butler, Herman Goossens, Theo J Verheij, and Paul Little for the GRACE consortium. Br J Gen Pract 2014 64:e75-80.

Antibiotics are of limited overall clinical benefit for uncomplicated lower respiratory tract infection (LRTI) but there is uncertainty about their effectiveness for patients with features associated with higher levels of antibiotic prescribing.

The aim of this study was to estimate the benefits and harms of antibiotics for acute LRTI among those producing coloured sputum, smokers, those with fever or prior comorbidities, and longer duration of prior illness by analyzing data from a randomised controlled trial of antibiotic placebo for acute LRTI in primary care.

Two thousand and sixty-one adults with acute LRTI, where pneumonia was not suspected clinically, were given amoxicillin or matching placebo. The duration of symptoms, rated moderately bad or worse (primary outcome), symptom severity on days 2–4 (0–6 scale), and the development of new or worsening symptoms were analysed in pre-specified subgroups of interest. Evidence of differential treatment effectiveness was assessed in prespecified subgroups by interaction terms.

No subgroups were identified that were significantly more likely to benefit from antibiotics in terms of symptom duration or the development of new or worsening symptoms. Those with a history of significant comorbidities experienced a significantly greater reduction in symptom severity between days 2 and 4 (interaction term –0.28, P = 0.003; estimated effect of antibiotics among those with a past history –0.28 [95% confidence interval = –0.44 to –0.11], P = 0.001), equivalent to three people in 10 rating symptoms as a slight rather than a moderately bad problem. For subgroups not specified in advance antibiotics provided a modest reduction in symptom severity for non-smokers and for those with short prior illness duration (<7 days), and a modest reduction in symptom duration for those with short prior illness duration. A Kaplan–Meier survival curve is shown for those with green sputum (Figure 4).

In conclusion, there is no clear evidence of clinically meaningful benefit from antibiotics in the studied high-risk groups of patients presenting in general practice with uncomplicated LRTIs where prescribing is highest. Any possible benefit must be balanced against the side-effects and longer-term effects on antibiotic resistance.

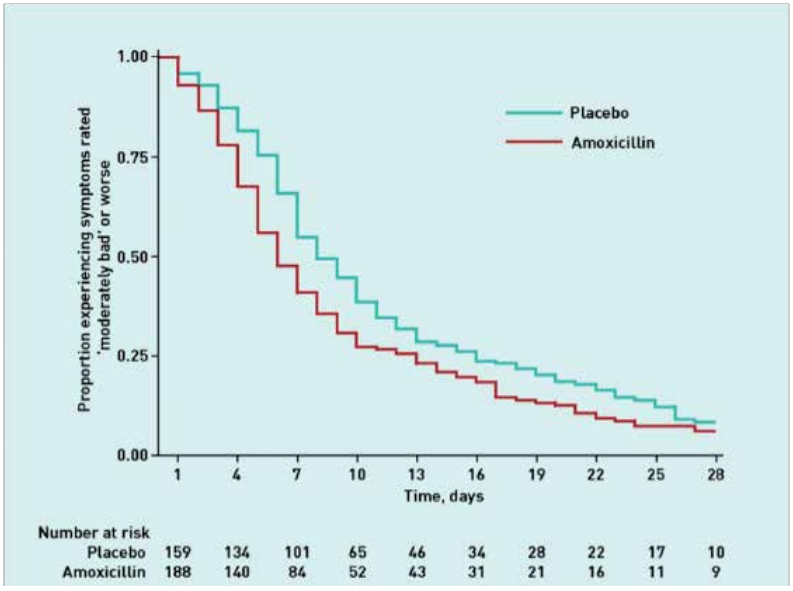


Figure 4. Kaplan–Meier survival curve for the duration of symptoms rated moderately bad or worse in patients with green sputum. Although a separation of the survival curves may be seen, there is a modest impact on the median and interquartile range of symptom duration.

Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough.

Samuel Coenen, Nick Francis, Mark Kelly, Kerenza Hood, Jacqui Nuttall, Paul Little, Theo J Verheij, Hasse Melbye, Herman Goossens, Christopher C Butler for the GRACE Project Group. PLoS One 2013 23;8:e76691.

Outpatients with acute cough who expect, hope for or ask for antibiotics may be more unwell, benefit more from antibiotic treatment, and be more satisfied with care when they are prescribed antibiotics. Clinicians may not accurately identify those patients.

The objectives of this study were to explore whether patient views (expecting, hoping for or asking for antibiotics) are associated with illness presentation and resolution, whether patient views are accurately perceived by clinicians, and the association of all these factors with antibiotic prescribing and patient satisfaction with care. Therefore, a prospective observational study of 3402 adult patients with acute cough presenting in 14 primary care networks was set-up. Correlations and associations tested with multilevel logistic regression and McNemar 's tests, and Cohen's Kappa, positive agreement (PA) and negative agreement (NA) were calculated as appropriate.

1,213 (45.1%) patients expected, 1,093 (40.6%) hoped for, and 275 (10.2%) asked for antibiotics (Figure 5). Clinicians perceived 840 (31.3%) as wanting to be prescribed antibiotics (McNemar's test, $p<0.05$). Their perception agreed modestly with the three patient views (Kappa's = 0.29, 0.32 and 0.21, PA's = 0.56, 0.56 and 0.33, NA's = 0.72, 0.75 and 0.82, respectively). 1,464 (54.4%) patients were prescribed antibiotics. Illness presentation and resolution were similar for patients regardless their views. These associations were not modified by antibiotic treatment. Patient expectation and hope (OR:2.08, 95% CI:[1.48,2.93] and 2.48 [1.73,3.55], respectively), and clinician perception (12.18 [8.31,17.84]) were associated with antibiotic prescribing. 2,354 (92.6%) patients were satisfied. Only those hoping for antibiotics (Figure 5) were less satisfied when antibiotics were not prescribed (0.39 [0.17,0.90]).

In conclusion, patient views about antibiotic treatment were not useful for identifying those who will benefit from antibiotics. Clinician perceptions did not match with patient views, but particularly influenced antibiotic prescribing. Patients were generally satisfied with care, but those hoping for but not prescribed antibiotics were less satisfied. Clinicians need to more effectively elicit and address patient views about antibiotics.

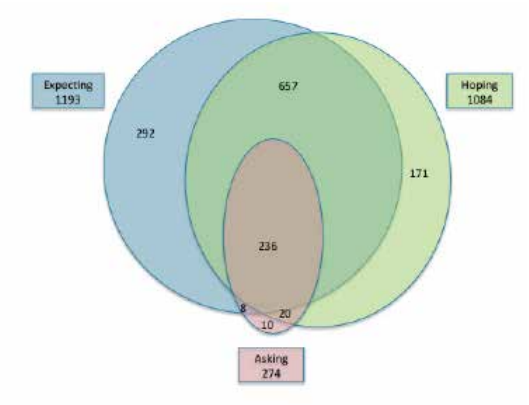


Figure 5. Venn diagram of expectations, hopes and requests for antibiotics in adult outpatients with acute cough. Figures differ from text due to missing data.

Fourth Steering Committee Meeting and eighth ESF Science Meeting

On October 3rd, the fourth TRACE Steering Committee Meeting was held in Antwerp, Belgium. This meeting preceded the ESF Science Meeting "General Practice Research on Infections Network Meeting 2014" held at the same venue on 3 and 4 October. Both meetings were very well attended, with in total over 60 participants from 13 different countries.

During the Steering Committee meeting TRACE involvement in PREPARE (see p.1), in particular the primary care studies, was a major topic. In addition, the Steering Committee agreed to support Open Access publication fees for TRACE related papers, to continue TRACE support for each of the GRACE Database (coordinated in Utrecht) and the GRACE Biobank (coordinated in Antwerp) and to further develop a realistic plan of (new)activities, including the development and dissemination of an educational package based on the results of GRACE (www.grace-lrti.org), CHAMP (www.champ-antibiotics.org) and HAPPY AUDIT (www.happyaudit.org).

Mark Ebell

The participants of the ESF Science Meeting, GRIN 2014, were welcomed by the Dean of the Faculty of Medicine and Health Sciences of the University of Antwerp (Belgium), Paul Van Royen. They enjoyed over 30 succinct presentations separated into sessions on 'urinary tract infections', 'aetiology and management of respiratory tract infections', 'determinants of antibiotic prescribing', 'patients, antibiotics and interventions' and 'infections in children' and a keynote presentation by Mark Ebell of the College of Public Health of the University of Georgia (US) on diagnosis and treatment of influenza in primary care. He proposed a framework to study infectious diseases in primary care by answering several relevant questions to improve their management. Whereas for influenza many questions have been answered to date, for many other common infections in primary care evidence is lacking, e.g. on the natural history and prognosis. 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 TRACE Steering Committee Meeting as well as the next GRIN Meeting will be held in Galway, Ireland, on 2-3 October 2015.

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