ERJ Express. Published on March 15, 2011 as doi: 10.1183/09031936.00133910

Antibiotic prescribing for discoloured sputum in acute cough/LRTI

Christopher C Butler **Professor** Department of Primary Care and Public Health, School of Medicine, Cardiff University. Mark J Kelly **Statistician** Department of Primary Care and Public Health, School of Medicine, Cardiff University. Kerenza Hood **Professor** Department of Primary Care and Public Health, School of Medicine, Cardiff University. Tom Schaberg **Professor** Center of Pneumology, Deaconess Hospital Rotenburg. Hasse Melbye **Professor** General Practice Research Unit, Institute of Community Medicine, University of Tromsø. Mateu Serra-Prat **MD** Unitat de Recerca, Hospital de Mataró. Francesco Blasi **Professor** 11Respiratory Medicine Section, Dipartimento Toraco-Polmonare e Cardiocircolatorio, University of Milan, IRCCS Fondazione Ca` Granda, Italy. Paul Little **Professor** School of Medicine, University of Southampton. Theo Verheij **Professor** University Medical Center Utrecht, Julius Center for Health, Sciences and Primary Care. Sigvard Mölstad **Professor** Department of Medical and Health Sciences, Linköping University. Maciek Godycki-Cwirko **Physician** Department of Family and Community Medicine, Medical University of Łódź. Peter Edwards **Physician** Ely Bridge Surgery, Ely, Cardiff. Jordi Almirall **Professor** Unitat de Cures Intensives, Hospital de Mataró. Antoni Torres **Professor** Pneumology Department, Clinic Institute of Thorax (ICT), Hospital Clinic of Barcelona- Insitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)- University of Barcelona (UB)- Ciber de Enfermedades Respiratorias (Ciberes) Villarroel 170, 08036 Barcelona, Spain. Supported by: 2009 SGR 911, Ciber de Enfermedades Respiratorias (Ciberes CB06/06/0028), the Ciberes is an iniciative of the ISCIII Ulla-Maija Rautakorpi **Senior medical officer** Finnish Office for Health

Technology Assessment Finohta, National Institute for Health and Welfare THL, Tampere Office. Jacqui Nuttall **Senior trial manager** Department of Primary Care and Public Health, School of Medicine, Cardiff University. Herman Goossens **Professor** Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute (VAXINFECTIO) , University of Antwerp. Samuel Coenen **Professor** Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute (VAXINFECTIO) , University of Antwerp.

Corresponding Author

Christopher C Butler Primary Care and Public Health, Cardiff University

Email: butlercc@Cardiff.ac.uk

Keywords: Acute cough, antibiotic resistance, antibiotic treatment, lower respiratory tract infection, primary care sputum

Word Count: 3,611

Abstract

We investigated whether discoloured sputum and feeling unwell is associated with antibiotic prescribing and benefit from antibiotic treatment for acute cough/lower respiratory tract infection in a prospective study of 3402 adults. in 13 countries.

A two-level model investigated the association between producing discoloured sputum or feeling generally unwell and an antibiotic prescription. A three-level model investigated the association between an antibiotic prescription and symptom resolution.

Patients producing discoloured sputum were prescribed antibiotics more frequently than those not producing sputum (OR: 3.2, 95% CI: [2.1, 5.0]), unlike those producing clear/white sputum (OR: 0.95, 95% CI: [0.61,1.48]). Antibiotic prescribing was not associated with greater rate or magnitude of symptoms score resolution (as measured by 13 item scale completed by patients each day) among those who: produced yellow (Coefficient: 0.00, p-value: 0.68) or green sputum (Coefficient: -0.01, p-value: 0.11); reported any of three categories of feeling unwell; produced discoloured sputum and felt generally unwell (Coefficient: -0.01, p-value: 0.19).

Adults with acute cough/LRTI presenting in primary care with discoloured sputum were prescribed antibiotics more often compared to those not producing sputum. Sputum colour, alone or together with feeling generally unwell was not associated with recovery or benefit from antibiotic treatment.

Trial Registration

Registry: Clinicaltrials.gov. Clinical trial no. : NCT00353951 http://clinicaltrials.gov/ct2/show/record/NCT00353951?cond=%22Cough%22&rank=10

Introduction

Acute cough is one of the commonest reasons for consulting and for prescribing antibiotics in primary care.(1-3) Feasible clinical strategies are needed for more effective targeting of antibiotic treatment to those who will receive meaningful benefit to contain antimicrobial resistance, reduce cost, promote self-care and reduce unnecessary risk from side effects. (4, 5) Physicians commonly ask their patients about the colour of their sputum and how unwell they are feeling to inform their decision whether or not to prescribe an antibiotic for acute cough, based on the assumption that purulence is more likely to reflect a bacterial cause and predict improved outcomes from antibiotics. (6-8) Clinicians regard patients who feel both systemically unwell and who also produce discoloured sputum at even higher priority for an antibiotic prescription. (9-11) Guidelines identify purulent sputum as one of a cluster of clinical features that should alert clinicians to possible serious lung infection. (12) Patients, too, are more likely to associate purulence with the need for antibiotic treatment. (13, 14)

However, it is not clear which symptoms and clinical signs predict improved outcomes from antibiotic treatment, and the usefulness of sputum colour in predicting benefit from antibiotic treatment among patients with acute cough is controversial. (15, 16) Increasing diagnostic uncertainty is associated with increased unnecessary antibiotic prescribing. (17) Using data from our large prospective observational study of the presentation, management and outcome of acute cough, (3) we therefore explored whether adult patients consulting in general practice with acute cough and who produced discoloured sputum and/or were feeling generally unwell were more likely to be prescribed antibiotics. We

also examined whether the symptom score resolution differed between these patients and those who did not produce discoloured sputum and/or were feeling generally unwell, and whether this was associated with antibiotic treatment.

Materials and methods

Study subjects

Eligible patients were aged 18 years and over consulting with an illness where an acute or worsened cough was the main or dominant symptom, or had a clinical presentation that suggested a lower respiratory tract infection (LRTI), with a duration of up to and including 28 days. We asked clinicians to attempt to enrol consecutive eligible patients from October – November 2006, and late January – March 2007. However, the networks were not able to ask clinicians to complete a log of all eligible patients. Ethical approval was obtained in each network.

Study Design

This was a further analysis from a prospective observational study in 14 primary care networks in 13 European countries with clinicians recording symptoms on presentation and management. More details on this observational GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) study of acute cough have been reported elsewhere. (3) The objectives of the study were to investigate whether discoloured sputum and feeling unwell is associated with antibiotic prescribing and predicts benefit from antibiotic treatment for acute cough. The study sample size was based on an estimate of a probability of 50% for certain events such as treatment decisions (50% is the most conservative estimate of probabilities in statistical terms; more common or more rare events would give more power). This required a total sample size of 270 per network to give 95% confidence

intervals of 44 to 56 around detecting that 50% probability *within* each network. This study uses all available data. The study was not therefore specifically powered for this analysis: we used all available data and provide confidence intervals for interpretation of the precision of our estimates.

Methods

Clinicians recorded aspects of patients' history, symptoms, co morbidities (diabetes, chronic lung disease including Chronic Obstructive Pulmonary Disease (COPD), cardiovascular disease, and presence of asthma), clinical findings, and their management including antibiotic prescription on a case report form (CRF). One of the symptoms that clinicians recorded was whether patients felt generally unwell. Clinicians rated whether this symptom constituted 'no problem', a 'mild problem', a 'moderate problem' or a 'severe problem' for the patient. Clinicians indicated the presence or absence of 13 other symptoms in the same way (cough, sputum production, shortness of breath, wheeze, coryza, fever during this illness, chest pain, muscle aching, headache, disturbed sleep, interference with normal activities, confusion/disorientation and diarrhoea). They were also asked to record the colour of the patient's sputum (if present) as clear, white, yellow, or green. Clear or white sputum is denoted normal and yellow and green is denoted discoloured. Clinicians were not routinely asked to check for themselves the patient's sputum colour, as we wanted data to best represent everyday practice. Clinicians recorded their management, including antibiotic prescribing decisions for each patient.

Patients were given a symptom diary. They were asked to rate 13 symptoms each day until recovery (or for 28 days if symptoms were ongoing) on a 7-point scale comprising the following responses: “normal/not affected”, “very little problem”, “slight problem”, “moderately bad”, “bad”, “very bad”, “as bad as it can be”. This approach to outcome measurement has been used in other studies of acute cough/LRTI and has been found to be responsive to change and discriminating. (18) Patients rated the same symptoms as the clinicians except for confusion/disorientation and diarrhoea. They were, in addition, asked about interference with social activities. A patient-rated total symptom severity score was calculated by summing the scores for each symptom and scaling it so that it could be interpreted as a percentage symptom severity score.

The CRF and patient diary were translated into local languages and then back-translated into English for accuracy checks by the central study team. Final face validity checks were made with practicing bilingual clinicians.

Analysis

We used a two-level (patients nested within clinicians) logistic regression with antibiotic prescribing as the outcome to investigate whether patients with discoloured sputum (yellow, green or yellow/green) or normal sputum were more likely to be prescribed antibiotics than those producing no sputum and whether patients feeling generally unwell (comprising those who reported feeling mildly, moderately or severely unwell) were more likely to be prescribed antibiotics than those not feeling generally unwell.

A three-level (daily symptom scores nested within patients nested within clinicians) hierarchical ARMA (1,1) model (see box 1)(19) was fitted to the logged (to improve model fit) scaled, daily symptom scores to investigate whether patient subgroups had significantly different symptom severity at baseline and symptom score resolution over time. These subgroups were: those reporting yellow sputum, those reporting green sputum, those who felt mildly unwell, those who felt moderately unwell, those who felt severely unwell, and finally those who had discoloured sputum (yellow or green) *and* who felt generally unwell. The reference category for these analyses was those not producing sputum and who did not report feeling generally unwell. Interaction terms were fitted for each of these subgroups to investigate whether being prescribed an antibiotic was associated with a difference in symptom resolution. This was investigated using a three-way interaction term between belonging to one of these subgroups, being prescribed an antibiotic and time measured in days.

These analyses controlled for clinical presentation by including patient information on 12 of the 14 clinician-recorded symptoms (cough was excluded as it was present in 99.8% of cases and feeling generally unwell is one of the symptoms of interest), temperature, age, co-morbidities (cardiovascular, respiratory including COPD, and COPD on its own, diabetes, and asthma), the number of days waited before presentation, smoking status and network. We did not sum clinician ratings of symptoms into a scale. Co-morbidities including COPD and asthma were ascertained by the responsible treating clinician from their knowledge of the patient and the clinical record. Additional diagnostic tests

were not done for the purposes of this study. No imputation was performed on the patient-reported symptom scores.

To illustrate the differences in symptom resolution between subgroups and between those prescribed antibiotics or not within the subgroups, estimated patient-reported symptom scores on day seven are presented for each of the subgroups split by whether they were prescribed antibiotics or not. We performed sensitivity analyses to investigate differences in patient-reported symptom score resolution between those prescribed and those not prescribed antibiotics in three subgroups of patients with discoloured sputum *and* who were feeling generally unwell; i.e. those who also had COPD, those who also had asthma, and those who were over 65 years old.

Results

A total of 3402 patients were recruited by 387 practitioners. Six networks included 270 patients or more, and all included over 100. Four patients were later found to be ineligible and were therefore excluded from further analysis. CRFs were completed for 3368 (99%) and diary data was obtained from 2714 (80%) patients (Figure 1).

Patients who returned the diary data were generally older (median age 47 years vs. 36 years) and more frequently prescribed antibiotics (54% vs. 46%), but were otherwise similar (Table 2).

We analysed data from 2,419 patients with both useable CRF and patient diary data. The following variables had some missing values: phlegm production (75), shortness of breath (4), wheeze (6), coryza (11), fever (18), chest pain (7), muscle aching (11), headache (8), disturbed sleep (18), feeling generally unwell (13), interference in normal activities (13), confusion (4), diarrhoea (5), temperature (20), smoking status (3), and sputum colour (57). Of these 638 (26.4%) were producing yellow sputum and 451 (18.6%) were producing green sputum, 1940 (80.2%) were feeling generally unwell, and 897 (37.1%) were producing yellow or green sputum *and* also feeling generally unwell. 137 (5.7%) had COPD. Those who the clinician rated as feeling generally unwell (mild (n=734, 30.3%), moderate (n=947, 39.1%) and severe (n=259, 10.7%)) also had higher self-rated symptom severity scores for day one of the self compete diary compared to those for whom the clinician recorded that feeling generally unwell

was ‘not a problem’. This suggests that clinicians rating of illness severity was congruent with patients own assessment of the severity of their symptoms.

Those producing normal sputum were not prescribed antibiotics more frequently than those not producing sputum (OR: 0.95, 95% CI: [0.61,1.48]) Those with discoloured sputum were more likely to be prescribed antibiotics compared to those not producing sputum (OR: 3.2, 95% CI: [2.1, 5.0]). Those feeling generally unwell (any category) were not prescribed antibiotics any differently than those not feeling generally unwell (overall p-value = 0.24)

Online Table 1 shows the symptom severity at baseline and symptom resolution over time for the various subgroups and whether this was associated with antibiotic treatment for both adjusted (adjusted for clinician recorded symptoms, temperature, age, comorbidities, number of days waited before presentation and smoking status) and unadjusted models. The three subgroups of feeling generally unwell (mild, moderate or severe) were observed to have higher symptom severity at baseline and to recover slightly faster than those who were recorded as not feeling generally unwell. However, within these subgroups those treated with antibiotics were no different in terms of symptom severity or resolution compared to those not treated with antibiotics (online table 1).

Sputum colour (yellow or green) was not associated with symptom severity at baseline nor with resolution over time in the adjusted models. Moreover, producing discoloured sputum *and* feeling generally unwell was not associated

with symptom severity at baseline or resolution over time. All of this information is presented in online table 1.

Table 3 provides estimates of the differences in percentage symptom severity scores based on the coefficients presented in online table 1. These differences in symptom resolution were small (Table 3) with the estimated symptom severity scores on day 7 ranging between 3.9% (green sputum group) and 5.1% (yellow/green *and* feeling severely unwell group) for those who were not prescribed antibiotics and between 3.9% (yellow/green sputum *and* feeling mildly generally unwell) and 5% (yellow/green *and* feeling severely unwell group). The differences between those who were and were not prescribed antibiotics were not statistically significant. The estimated symptom resolution for each subgroup is illustrated in figure 2.

Antibiotics were prescribed for 67.4% (n = 124) of patients with COPD, 57.9% (n = 195) of patients with asthma, and 54.5% (n = 265) of patients aged over 65 years. In these subgroups of patients symptom resolution for patients with discoloured sputum *and* who were feeling generally unwell was not associated with antibiotic treatment (final three rows of online Table 1).

Discussion

Summary of main results

This is the only large prospective study in primary care to have examined the relationship between sputum colour and/or feeling generally unwell and symptom resolution and whether or not this was associated with antibiotic treatment. We found that adults consulting in primary care with an acute cough and who produce discoloured sputum are more likely to be prescribed antibiotics. However, we also found no clinically meaningful associations between sputum colour and/or feeling generally unwell with symptom resolution. Furthermore, symptom resolution was *not* associated with antibiotic treatment in patients with discoloured sputum *and* who were feeling generally unwell and those who belonged to both of these subgroups. The biggest difference between those who were and were not treated with antibiotics was less than one half of a percentage point on a symptom severity scale (table 3).

We have previously considered the relationship between antibiotic prescribing in general and prescribing by antibiotic class with outcomes for all patients, and found no clinically meaningful association with patients outcomes in this group. (3, 20)

Strengths and weaknesses

An advantage of this observational study design is that treatment decisions were left up to the responsible clinician, unlike in a randomised study, making our results more applicable to actual practice. Not requiring additional non-routine investigations also makes this study more applicable to everyday practice.

Randomising patients with discoloured sputum to either receive or not receive antibiotic treatment could increase internal validity, but some patients might not wish to participate if they risk being randomising to a particular treatment or to placebo when they feel particularly unwell. Furthermore, there is some evidence that older patients may derive benefit from antibiotic treatment. (21)

We did not attempt to infer causality from these data. Our analyses were designed to identify associations.

We included a large number of patients from a variety of primary care settings across Europe with close to complete ascertainment of baseline characteristics by clinicians and with an 80% return rate of patient's self complete follow-up symptom diary data. We were able to control for several known possible confounders (illness severity at the time of the index consultation, standardised measurement of body temperature, patient age, number of days ill before the index consultation, diabetes, cardiovascular or respiratory (including COPD and asthma) co morbidities, and smoking status). A wide range of physician assessed symptoms and signs were individually included in our models. However, this observational design could not account for unknown confounders. The patients in this study represent the larger, but milder end of the clinical spectrum of patients with acute cough, and the findings cannot be uncritically applied to patients with more severe lung disease, and who, for example, may have well defined acute exacerbations of COPD. However, our sensitivity analysis for the patients with COPD, those with asthma, and those aged over 60 showed sputum colour *and* feeling generally unwell was not associated with benefit from

antibiotic treatment. In these subgroups of patients therefore, antibiotic treatment was not associated with greater rate or magnitude of symptoms resolution, even in those with discoloured sputum and who were feeling generally unwell (final three rows of online Table 1). We did not record data on sputum consistency. Sputum colour was determined, as is common in routine practice, by asking the patient rather than confirming colour using charts, which adds to applicability of findings to everyday primary care. We did not monitor change in sputum colour over time, as our goal was to explore the prognostic usefulness of sputum colour at the time of presentation. The clinicians who recruited patients also recorded data on them. Ideally, severity assessment would have been separated from management decisions, but it was not possible to have researchers at each participating practice, which is usually the case with most primary care research of this nature. However, patient outcome was not assessed by recruiting clinicians and as this was not a randomised study, ascertainment bias is unlikely. Clinicians did not keep a log of all eligible patients and those approached and the outcome as this was considered too burdensome in a pragmatic study. We only considered antibiotic treatment at the initial consultation in our analyses. As our main study questions related to associations between symptoms, antibiotic prescription and outcomes, patient adherence to antibiotic prescriptions were not considered in the analysis.

Comparison with existing literature

We found that patients presenting with acute cough in primary care who have discoloured sputum are more likely to be prescribed antibiotics than those not producing sputum or producing white sputum. This confirms previous findings

that physicians are more likely to prescribe antibiotics to patients with presumed respiratory tract infections (RTIs) who produce purulent sputum. Coenen and colleagues analysed data from 72 Flemish general practitioners (GPs) on the management of 1448 patients with acute cough. The presence of sputum was associated with an increased risk of antibiotic prescribing independent of patient and clinician characteristics (OR 2.5, 95%CI 1.62-3.92). (22) Fisher and colleagues directly observed 30 GPs in Germany manage 237 patients with RTIs. Purulent sputum was associated with an increased chance of antibiotic prescribing (OR 2.1, 95% CI 1.1-4.1). (10) In another study from Germany, Hummers-Pradier and colleagues found increased antibiotic prescribing for RTIs when patients had yellow or green sputum (OR 4.4, 95% CI 1.84-10.69). (7) In the Netherlands, discoloured sputum was related to antibiotic treatment and one of the reasons for overprescribing in LRTI. (23) In the US, Gonzales and colleagues found antibiotic prescribing for upper respiratory tract infection was increased when patients produced green sputum, (OR 4.8, 95% CI 2.4-11.1), (24) and Doss and colleagues found antibiotic prescribing increased in association with smokers coughing up green or yellow sputum (OR 2.5, 95% CI 1.7-3.8). (25) Altiner and colleagues obtained sputum samples from 241 patients with acute cough in primary care and found 136 of these were coloured yellow or greenish. (26) Only 28 samples yielded pathogens on culture. The sensitivity of yellowish or greenish sputum as a test for bacterial infection was 0.79 (95%CI 0.63-0.94) and the specificity 0.46 (95%CI 0.038-0.53).

We know from a trial in volunteers that antibiotic resistant oral streptococci persist for at least 180 days as a consequence of antibiotic exposure.(27) In that

study, follow up was for up to 28 days, so was unable to capture either possible harms from resistance or benefits from reducing bacterial colonization and possible subsequent inflammation.

None of these studies explored the relationships between sputum colour and outcomes. We were not able to identify any previous large prospective studies examining the associations between sputum colour or feeling generally unwell and outcome and whether or not this was associated with antibiotic treatment.

Previous trials have however showed no meaningful benefit from antibiotics treatment, on average, for patients consulting in primary care with acute cough and purulent sputum. (18, 21, 28, 29) The European Respiratory Society guidelines for the management of adult lower respiratory tract infections recommend that for patients managed outside hospital, antibiotics should be considered only for those with suspected or definite pneumonia, selected exacerbations of COPD, and in patients with acute bronchitis and with an age over 75 years and fever, and/or cardiac failure, insulin dependent diabetes, and serious neurological disorders. (30) The US Centers for Disease Control and Prevention Physician Information Sheet on Acute Cough Illness (Acute Bronchitis) recommends against empiric antibiotic treatment (http://www.cdc.gov/getsmart/campaign-materials/info-sheets/adult-acute-cough-illness.html). They cite evidence that over 95% of patients with purulent sputum do not have symptoms of pneumonia. (31)

Implications for policy and practice

This study focused on a broad category of adult patients, namely those with acute cough consulting in a broad range of general medical practice settings in Europe. The findings suggest that physicians should not rely on sputum colour, either on its own or in conjunction with patients feeling generally unwell, when deciding whether or not to prescribe an antibiotic for such patients. These data will have relevance to a large number of health care encounters. Acute cough is the largest single acute cause of consultation in primary care in the UK . (1) In the US, about there were about 10 million office visits in for acute bronchitis 1997. (32) Implementing this evidence is likely to reduce antibiotic prescribing for those with acute cough who are unlikely to benefit from antibiotic treatment and thus contribute to containing antibiotic resistance. (26)

Acknowledgments

We acknowledge the entire GRACE team for their diligence, expertise, and enthusiasm. The GRACE team are: Zseraldina Arvai, Zuzana Bielicka, Alicia Borras, Curt Brugman, Jo Coast, Mel Davies, Kristien Dirven, Iris Hering, Judit Holczerné, Kristin Alise Jakobsen, Bernadette Kovaks, Christina Lannering, Frank Leus, Katherine Loens, Michael Moore, Magdalena Muras, Carol Pascoe, Richard Smith, Jackie Swain, Paolo Tarsia, Kirsi Valve, Robert Veen, and Tricia Worby. We thank all the clinicians and patients who consented to be part of GRACE, without whom this study would not have been possible.

Competing interests

All authors have completed a statement of interest form.

Funding

This study was funded by 6th Framework Programme of the European Commission (LSHM-CT-2005-518226). The South East Wales Trials Unit is funded by the Wales Office for Research and Development. The funders had no role in the design and conduct of the study, nor the collection, management, analysis or interpretation of the data, nor in the preparation, review or approval of this manuscript. Chris Butler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He is the guarantor.

Ethical approval

Ethic review committees in each country approved the study.

References

1. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. Brit J Gen Pract. 2005 Aug;55(517):603-8.

2. Mainous AG, Hueston WJ, Davis WP, Pearson WS. Trends in antimicrobial prescribing for bronchitis and upper respiratory infections among adults and children. Am J Public Health. 2003 Nov;93(11):1910-4.

3. Butler CC, Hood K, Verheij T, Little P, Melbye H, Nuttall J, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. Brit Med J. 2009 Jun 23;338:-.

4. Butler CC, Dunstan F, Heginbothom M, Mason B, Roberts Z, Hillier S, et al. Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices. Brit J Gen Pract. 2007 Oct;57(543):785-92.

5. Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory infections in primary care. Lancet Infect Dis. 2007 Nov;7(11):749-56.

6. Gonzales R. A 65-year-old woman with acute cough illness and an important engagement. Jama-J Am Med Assoc. 2003 May 28;289(20):2701-8.

7. Hummers-Pradier E, Pelz J, Himmel W, Kochen MM. Treatment of respiratory tract infections- a study in 18 general practices in Germany. European Journal of General Practice. 1999;5:15-20.

8. Storring RA. Antibiotics for coughs and colds - Hello, virus. Brit Med J. 2008 Aug 23;337(7667):-.

9. Coenen S, Michiels B, Van Royen P, Van der Auwera JC, Denekens J. Antibiotics for coughing in general practice: a questionnaire study to quantify and condense the reasons for prescribing. BMC Fam Pract. 2002 Sep 9;3:16.

10. Fischer T, Fischer S, Kochen MM, Hummers-Pradier E. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. BMC Fam Pract. 2005 Feb 7;6(1):6.

11. Wigton RS, Darr CA, Corbett KK, Nickol DR, Gonzales R. How do community practitioners decide whether to prescribe antibiotics for acute respiratory tract infections? J Gen Intern Med. 2008 Oct;23(10):1615-20.

12. Morice AH, McGarvey L, Pavord I, Cough BTS. Recommendations for the management of cough in adults. Thorax. 2006 Sep;61:I1-I24.

13. Cals JW, Boumans D, Lardinois RJ, Gonzales R, Hopstaken RM, Butler CC, et al. Public beliefs on antibiotics and respiratory tract infections: an internet-based questionnaire study. Br J Gen Pract. 2007 Dec;57(545):942-7.

14. Mainous AG, Zoorob RJ, Oler MJ, Haynes DM. Patient knowledge of upper respiratory infections: Implications for antibiotic expectations and unnecessary utilization. J Fam Practice. 1997 Jul;45(1):75-83.

15. Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman LR, et al. Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: Background. Ann Intern Med. 2001 Mar 20;134(6):521-9.

16. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. Jama-J Am Med Assoc. 1997 Nov 5;278(17):1440-5.

17. McIsaac WJ, Butler CC. Does clinical error contribute to unnecessary antibiotic use? Med Decis Making. 2000 Jan-Mar;20(1):33-8.

18. Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection - A randomized controlled trial. Jama-J Am Med Assoc. 2005 Jun 22;293(24):3029-35.

19. Box G, Jenkins G. Time series analysis: forecasting and control. San Francisco: Holden-Day. 1976.

20. Butler CC, Hood K, Kelly MJ, Goossens H, Verheij T, Little P, et al. Treatment of acute cough/lower respiratory tract infection by antibiotic class and associated outcomes: a 13 European country observational study in primary care. J Antimicrob Chemoth. 2010;65(11):2472-8.

21. Verheij TJM, Hermans J, Mulder JD. Effects of Doxycycline in Patients with Acute Cough and Purulent Sputum - a Double-Blind Placebo-Controlled Trial. Brit J Gen Pract. 1994 Sep;44(386):400-4.

22. Coenen S, Michiels B, Renard D, Denekens J, Van Royen P. Antibiotic prescribing for acute cough: the effect of perceived patient demand. Brit J Gen Pract. 2006 Mar;56(524):183-90.

23. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJM. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. J Antimicrob Chemoth. 2005 Nov;56(5):930-6.

24. Gonzales R, Barrett PH, Steiner JF. The relation between purulent manifestations and antibiotic treatment of upper respiratory tract infections. J Gen Intern Med. 1999 Mar;14(3):151-6.

25. Dosh SA, Hickner JM, Mainous AG, Ebell MH. Predictors of antibiotic prescribing for nonspecific upper respiratory infections, acute bronchitis, and acute sinusitis - An UPRNet study. J Fam Practice. 2000 May;49(5):407-14.

26. Altiner A, Wilm S, Daubener W, Bormann C, Pentzek M, Abholz HH, et al. Sputum colour for diagnosis of a bacterial infection in patients with acute cough. Scand J Prim Health. 2009;27(2):70-3.

27. Amphora-Kumar S, Lammens C, Coenen S, Van Herck K, H. G. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007;10(369):482-90.

28. Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. Lancet. 2002 May 11;359(9318):1648-54.

29. Stott NC, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. Br Med J. 1976 Sep 4;2(6035):556-9.

30. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J. 2005 Dec;26(6):1138-80.

31. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough--a statistical approach. J Chronic Dis. 1984;37(3):215-25.

32. Schappert SM. Ambulatory care visits of physician offices, hospital outpatient departments, and emergency departments: United States, 1995. Vital Health Stat 13. 1997 Jun(129):1-38.

Figure 1: Patient flowchart

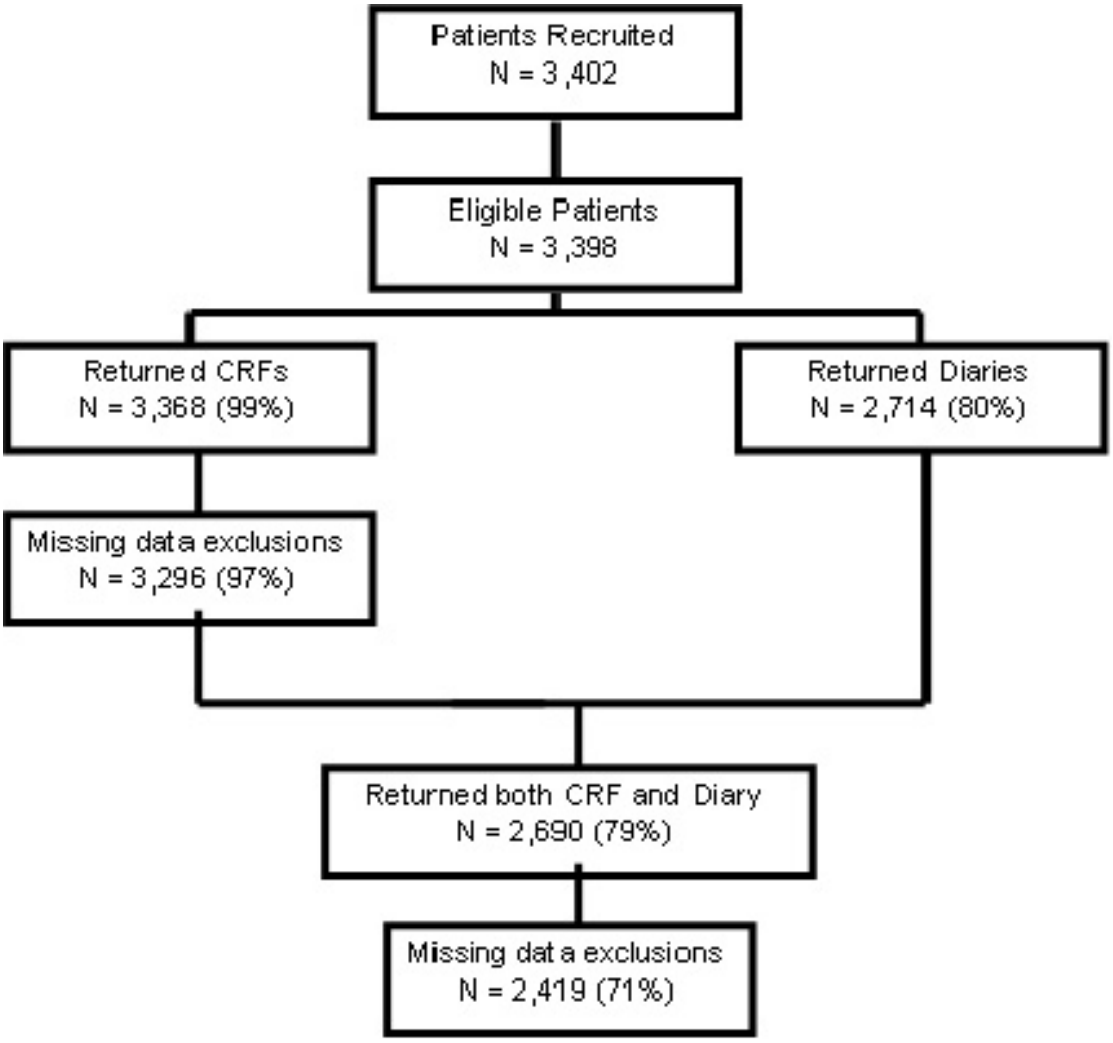


Table 1: Characteristics and antibiotic treatment of patients with acute cough by network

			Temperature					Comorbidities				Sputum colour		Feeling generally unwell			
Network	Patients n	Clinicians n	Normal % (n)	Under 36°C % (n)	Over 37.2°C % (n)	Age Median (IQR *)	Days waited, Median (IQR)	Diabetes % (n)	Respiratory % (n)	Cardio-vascular % (n)	COPD % (n)	Yellow % (n)	Green % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Antibiotics Prescribed % (n)
Cardiff	173	22	65.9 (114)	20.8 (36)	13.3 (23)	50.0 (38.0-61.0)	7 (5-10)	7.5 (13)	22.5 (39)	8.7 (15)	5.2 (9)	21.4 (37)	37.6 (65)	24.3 (42)	47.4 (82)	19.7 (34)	72.3 (125)
Southampton	139	22	80.6 (112)	7.2 (10)	12.2 (17)	47.0 (37.5-56.5)	9 (6-16)	4.3 (6)	17.3 (24)	7.9 (11)	1.4 (2)	18 (25)	34.5 (48)	31.7 (44)	43.2 (60)	12.9 (18)	64.7 (90)
Utrecht	155	31	58.1 (90)	29.0 (45)	12.9 (20)	56.0 (43.0-67.0)	10 (7-16)	8.4 (13)	25.8 (40)	12.3 (19)	12.3 (19)	20.6 (32)	25.8 (40)	22.6 (35)	35.5 (55)	7.7 (12)	43.9 (68)
Barcelona	153	25	62.7 (96)	19.6 (30)	17.6 (27)	45.0 (33.0-61.0)	6 (4-9)	3.9 (6)	10.5 (16)	5.9 (9)	2 (3)	13.7 (21)	19.6 (30)	47.1 (72)	18.3 (28)	2 (3)	19.6 (30)
Mataro	162	19	61.7 (100)	22.2 (36)	16.0 (26)	45.0 (29.25-63.0)	7 (5-9)	6.2 (10)	16.7 (27)	8 (13)	7.4 (12)	21 (34)	22.2 (36)	34.0 (55)	22.2 (36)	2.5 (4)	37 (60)
Rotenburg	171	19	57.3 (98)	28.7 (49)	14.0 (24)	41.0 (28.5-53.0)	6 (5-9)	5.3 (9)	13.5 (23)	5.8 (10)	4.7 (8)	28.7 (49)	17.5 (30)	15.2 (26)	40.4 (69)	21.6 (37)	33.9 (58)
Balatonfured	319	11	40.4 (129)	11.0 (35)	48.6 (155)	39.0 (26.0-50.0)	4 (4-5.5)	4.1 (13)	7.8 (25)	8.2 (26)	5.6 (18)	33.9 (108)	6.9 (22)	41.7 (133)	39.5 (126)	5.6 (18)	74.9 (239)
Antwerpen	122	25	56.6 (69)	16.4 (20)	27.0 (33)	46.5 (35.25-61.0)	6 (5-9)	2.5 (3)	19.7 (24)	5.7 (7)	12.3 (15)	30.3 (37)	12.3 (15)	32.0 (39)	42.6 (52)	11.5 (14)	27.9 (34)
Lodz	218	21	45.9 (100)	35.3 (77)	18.8 (41)	43.0 (29.0-55.0)	6 (5.8)	3.2 (7)	12.8 (28)	16.5 (36)	7.3 (16)	28.9 (63)	9.2 (20)	19.3 (42)	55.5 (121)	17 (37)	72.5 (158)
Milano	141	12	71.6 (101)	10.6 (15)	17.7 (25)	42.0 (35.0-59.0)	7 (5-10)	3.5 (5)	9.9 (14)	5.7 (8)	5 (7)	30.5 (43)	5.7 (8)	36.2 (51)	27.7 (39)	6.4 (9)	78.7 (111)
Jönköping	183	66	51.9 (95)	21.9 (40)	26.2 (48)	51.0 (37.0-61.0)	11 (8-17)	4.4 (8)	13.7 (25)	3.8 (7)	2.7 (5)	36.1 (66)	15.3 (28)	17.5 (32)	49.2 (90)	27.3 (50)	37.7 (69)
Tromsö	137	38	60.6 (83)	24.8 (34)	14.6 (20)	49.0 (37.0-56.0)	9 (6-12)	6.6 (9)	18.2 (25)	7.3 (10)	8 (11)	23.4 (32)	30.7 (42)	23.4 (32)	48.2 (66)	5.8 (8)	30.7 (42)
Helsinki	83	25	67.5 (56)	18.1 (15)	14.5 (12)	45.0 (33.0-54.5)	9 (6-16)	2.4 (2)	12 (10)	3.6 (3)	2.4 (2)	34.9 (29)	24.1 (20)	22.9 (19)	32.5 (27)	3.6 (3)	45.8 (38)
Bratislava	263	23	57.0 (150)	3.0 (8)	39.9 (105)	38.0 (26.0-49.0)	6 (5-8)	3.4 (9)	11 (29)	14.4 (38)	3.8 (10)	23.6 (62)	17.9 (47)	42.6 (112)	36.5 (96)	4.6 (12)	88.2 (232)

*** IQR: Interquartile range**

Table 2: Comparison of responders and non-responders to the diary on key patient characteristics

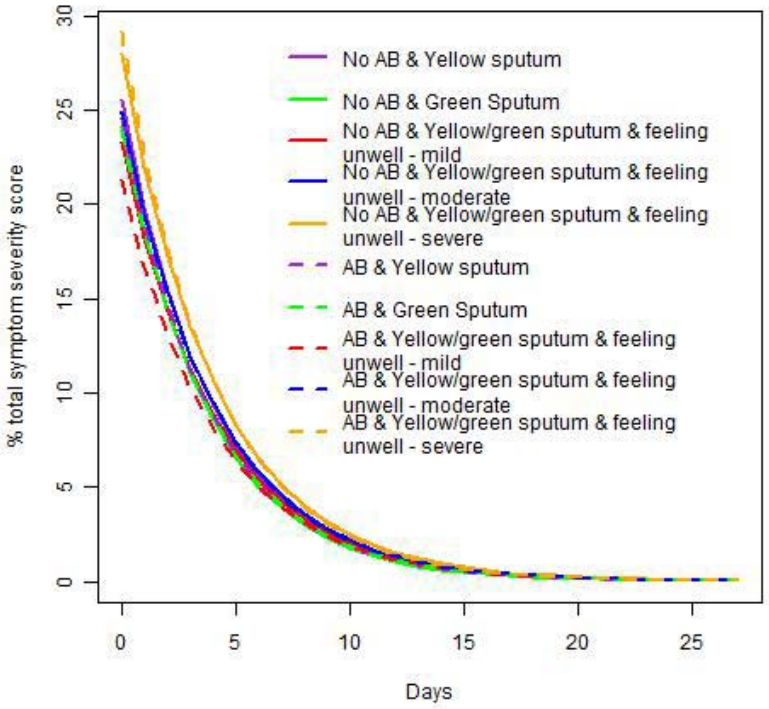
	Responders	Non-responders
Male, % (n)	36 (973)	38 (255)
Age, median (25%-75%)	47 (35, 60)	36 (27, 48)
Temperature, median (25%-75%)	36.8 (36.4, 37.2)	36.7 (36.2, 37.1)
Total clinician recorded symptom severity score, median (25%-75%)	26 (22, 31)	27 (23, 32)
Antibiotic prescription, % (n)	54 (1464)	46 (312)
Respiratory Comorbidity, % (n)	15 (395)	18 (120)
Diabetes Comorbidity, % (n)	5 (126)	2 (12)
Cardiovascular Comorbidity, % (n)	9 (240)	4 (26)
Discoloured Sputum, % (n)	45 (1223)	47 (321)
Yellow, % (n)	26 (689)	22 (150)
Green, % (n)	19 (498)	23 (159)
Bloodstained, % (n)	1 (36)	2 (12)
Feeling Generally Unwell,		

% (n)		
No problem, % (n)	21 (557)	22 (151)
Mild problem, % (n)	30 (803)	22 (146)
Moderate problem, % (n)	39 (1036)	40 (273)
Severe problem, % (n)	10 (281)	13 (90)
Total, n	2690	678

Table 3: Estimated patient recorded symptom scores (from patient diary data) for days 0 and 7 for subgroups of adult patients with acute cough stratified by whether they were prescribed antibiotics or not (from the 3 level hierarchical ARMA model).

	Day 0		Day 7	
	Not prescribed antibiotics	Prescribed antibiotics	Not prescribed antibiotics	Prescribed antibiotics
Yellow sputum	25.6	24.5	4.3	4
Green sputum	24.1	23.9	3.9	4
Yellow/green sputum & feeling generally unwell - mild	23.3	21.3	4.3	3.9
Yellow/green sputum & feeling generally unwell - moderate	24.9	24.9	4.5	4.5
Yellow/green sputum & feeling generally unwell - severe	28	29.1	5.1	5

Figure 2: Estimated patient recorded scaled symptom severity scores over 28 days after presentation for the subgroups of adult patients with acute cough (AB=antibiotic) (from the 3 level hierarchical ARMA model).



Online Table 1: Patient reported symptom score severity at baseline (day 0) and patient reported symptom score resolution over time in subgroups of adult patient with acute cough and its association with antibiotic treatment, both unadjusted and adjusted.

	Unadjusted				**Adjusted**			
	Symptom severity at baseline for those not treated with antibiotics	**Symptom resolution over time for those not treated with antibiotics**	**Symptom severity at baseline for those treated with antibiotics**	**Slope of symptom resolution over time for those treated with antibiotics**	**Symptom severity at baseline for those not treated with antibiotics**	**Symptom resolution over time for those not treated with antibiotics**	**Symptom severity at baseline for those treated with antibiotics**	**Slope of symptom resolution over time for those treated with antibiotics**
	Coefficient (95% CI[#])	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Sputum colour								
Yellow	0.34 (0.095,0.592) *	0.00 (-0.015,0.010)	-0.24 (-0.585,0.111)	0.00 (-0.014,0.021)	0.21 (-0.036,0.464)	0 (-0.016,0.009)	-0.20 (-0.548,0.146)	0 (-0.014,0.022)
Green	0.30 (0.043,0.563) *	-0.01 (-0.024,0.002)	-0.21 (-0.570,0.147)	0.01 (-0.004,0.033)	0.16 (-0.107,0.421)	-0.01 (-0.024,0.002)	-0.17 (-0.528 , 0.190)	0.01 (-0.004,0.033)
Feeling								

generally unwell								
No problem					Reference	Reference	Reference	Reference
Mild problem	0.43 (0.266,0.589) *	-0.01 (-0.023,-0.007) *	-0.27 (-0.524,-0.009)*	0.01 (-0.003,0.024)	0.34 (0.176,0.510)*	-0.02 (-0.025,-0.008)*	-0.25 (-0.509,0.007)	0.01 (-0.002,0.024)
Moderate problem	0.61 (0.449,0.772) *	-0.02 (-0.025,-0.009) *	-0.18 (-0.430,0.078)	0.01 (-0.006,0.020)	0.41 (0.238,0.580) *	-0.02 (-0.026,-0.009)*	-0.16 (-0.413,0.097)	0.01 (-0.006,0.020)
Severe problem	0.88 (0.637,1.115) *	-0.02 (-0.036,-0.011) *	-0.18 (-0.504,0.152)	0.00 (-0.016,0.018)	0.53 (0.275,0.782) *	-0.02 (-0.037,-0.012)*	-0.12 (-0.448,0.206)	0 (-0.015,0.019)
Discoloured sputum *and* feeling generally unwell	-0.31 (-0.576,-0.039) *	0.01 (-0.008,0.019)	0.31 (-0.062,0.683)	-0.01 (-0.031,0.007)	-0.22 (-0.491,0.046)	0.01 (-0.007,0.020)	0.25 (-0.125,0.619)	-0.01 (-0.032,0.006)
- COPD subgroup				-0.01 (-0.031,0.003)				0.01 (-0.031,0.05)
- asthma subgroup				0.02 (-0.011, 0.046)				0.01 (-0.015, 0.043)

- over 65s				0.02 (-0.007, 0.038)				0.01 (-0.010, 0.035)

Adjusted coefficients are based on a three-level hierarchical ARMA (1,1) model fitted to the logged daily symptom scores adjusted for clinician recorded severity of 12 of the 14 clinician-recorded symptoms (cough was excluded as it was present in 99.8% of cases and feeling generally unwell is one of the symptoms of interest), temperature, age, co-morbidities (cardiovascular, respiratory including COPD, and COPD on its own, and diabetes), the number of days waited before presentation, smoking status and network. To investigate whether being prescribed an antibiotic was associated with a difference in symptom severity at baseline and symptom resolution over time a three-way interaction term was fitted between belonging to one of the subgroups, time measured in days and being prescribed an antibiotic. Positive coefficients denote a higher symptom score to the reference category and negative coefficients denote lower symptom scores to the reference category.

CI : Confidence interval

* $p<0.05$

Box 1: ARMA model used to assess variation in patient outcome in relation to antibiotic prescribing

An ARMA (1,1) model comprises an **A**uto**R**egressive part and a **M**oving **A**verage part and expresses each observation as a combination of the two:

$$X_t = \varepsilon_t + X_{t-1} + \varepsilon_{t-1}$$

where X_t is the symptom severity score at time t, ε_t is the error term. This allows for each individual's symptom severity scores and the related error term to be correlated with the previous day.