Michael Moore, Beth Stuart, Samuel Coenen, Chris C Butler, Herman Goossens, Theo JM Verheij and Paul Little, on behalf of the GRACE consortium

Amoxicillin for acute lower respiratory tract infection in primary care:

subgroup analysis of potential high-risk groups

Abstract

Background

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.

Aim

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.

Design and setting

Secondary analysis of a randomised controlled trial of antibiotic placebo for acute LRTI in primary care.

Method

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.

Results

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.

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.

Keywords

antibiotics; primary health care; randomised controlled trial; respiratory infections.

INTRODUCTION

Acute uncomplicated lower respiratory tract infection (LRTI) is common in primary care practice. Most patients still receive antibiotics for LRTI,[1–4] despite the recommendations of most guidelines for limited prescribing.[5–7] The updated Cochrane review suggests some benefits from antibiotics; with a number needed to treat (NNT) of 6 for cough, nearly halving the number not improving, and no significant short-term harms.[8] However, the primary analysis of the largest trial to date, the genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections (Genomics to Combat Resistance against Antibiotics in Community-Acquired Lower Respiratory Tract Infections [GRACE] project [http://www.grace-lrti.org]) European multicentre placebo controlled trial of amoxicillin,[9] found that antibiotics did not meaningfully alter important outcomes; either symptom severity or duration of more severe symptoms. The development of new or worsening symptoms was, however, significantly different between groups, but the NNT was high (30) and was roughly equivalent to the number needed to harm.

The key question for clinicians and patients is whether the 'average' benefit from previous trials is meaningful, that is, whether the benefit or lack of benefit applies to all major clinical subgroups. Current guidelines recommend antibiotics in some situations, for instance older people and those with significant comorbidity,[7] and there is a suggestion from observational data that antibiotics confer some protection against pneumonia in older people.[3] However, prescribing is not limited to the identified at-risk groups.[4] Attempts to explain continued prescribing despite the recommendations of guidelines highlight key clinical factors that drive prescribing: abnormal chest sounds, fever, coloured sputum, and reported breathlessness,[10,11] in addition to non-medical reasons,[12,13] and perceived patient pressure.[14]

Thus the debate continues: clinicians and patients need to know whether antibiotics help in some subgroups, despite the average lack of benefit overall. This can only be addressed robustly by data from large trials, or, alternatively, by individual patient data meta-analyses. This secondary analysis of the GRACE trial aims to provide estimates of the benefits and harms of antibiotics for the pre-specified subgroups at risk listed below and following external referee, an additional subgroup of interest was identified: those with abnormal lung signs.

- smokers;
- those with green sputum;
- those with fever at baseline;

M Moore, MRCP, FRCGP, reader; **B Stuart**, PhD, research fellow; **P Little**, FRCGP, professor of primary care research, University of Southampton, Southampton, UK. **TJM Verheij**, MRCGP, professor of general practice, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands. **CC Butler**, FRCGP, professor of primary care, University of Oxford and Cardiff University, Cochrane Institutes of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, UK. **S Coenen**, DMSc, professor and head of the Centre for General Practice; **H Goossens**, professor of medical microbiology, Laboratory of Medical Microbiology, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium.

Address for correspondence

Michael Moore, Primary Medical Care, Aldermoor Health Centre, Aldermoor Close, Southampton, SO16 5ST, UK.

E-mail: mvm198@soton.ac.uk

Submitted: 11 July 2013; **Editor's response:** 6 September 2013; **final acceptance:** 29 October 2013.

This is the full-length article (published online 27 Jan 2014) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2014; DOI: 10.3399/bjgp14X677121**

How this fits in

In acute cough illness in primary care antibiotics confer little overall benefit. Secondary analysis of a large randomised trial failed to identify any subgroups with a clinically meaningful response to antibiotics.

- those with previous lung disease and/or significant other comorbidities;
- those with a longer prior duration of illness; and
- those with abnormal lung signs.

METHOD

Settings and patients

The study details are reported fully elsewhere.[9] In summary, participants were recruited between November 2007 and April 2010 by primary care practices in 16 networks from 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, and Wales).

Inclusion criteria

Participants were aged ≥18 years, with their first consultation with an acute cough (up to and including 28 days' duration) as the main symptom and where non-infective diagnoses were judged to be very unlikely (see exclusions), or alternatively where cough was not the most prominent symptom (for example, fever or malaise), but where the clinician considered acute LRTI was the main presenting diagnosis.

Exclusions

The following patients were excluded: those with a clinical diagnosis of community-acquired pneumonia,[15] based on focal chest signs (focal crepitations or bronchial breathing) and systemic features (high fever, vomiting, severe diarrhoea); those with a prior history of antibiotic use in the previous month; if the working diagnosis was a non-infective cause of cough; those unable to complete trial materials; those with penicillin allergy; those who were pregnant; and those with immunological deficiencies. Prior diagnosis of asthma, chronic obstructive pulmonary disease (COPD), or other comorbid conditions were not exclusion criteria.

Intervention

Patients who agreed to randomisation were allocated to receive either antibiotic (amoxicillin 1 g) or placebo three times a day for 7 days, by the clinician dispensing sequentially numbered pre-prepared randomised containers.

Data collection

All outcome data were collected blind to treatment allocation, comorbidities, clinical signs, and the severity of baseline symptoms reported by the patient (rating each symptom 'no problem', 'mild problem', a 'moderate problem', or a 'severe problem'). Participants completed a symptom diary daily until their symptoms had settled, up to a maximum of 28 days. The diary items recorded the severity of the following symptoms: cough, phlegm, shortness of breath, wheeze, blocked/runny nose, chest pain, muscle aches, headache, disturbed sleep, feeling generally unwell, fever, and interference with normal activities. Each symptom was scored from 0 to 6 (0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, 6 = as bad as it could be). The diary has previously been validated and is sensitive to change.[16] Participants were phoned after 4 days and contacted again after 4 weeks if the diary was not returned, to collect key outcomes by a short questionnaire or standardised phone call.

Main outcomes

Symptom duration. The primary outcome was the duration of more severe symptoms (symptoms rated 'a moderately bad problem' or worse by patients[17]) following the initial presentation, as this is easy to conceptualise for both patients and physicians.

Symptom severity. The mean diary score for all symptoms for study days 2–4 following the index consultation was specified, as this time period is when symptoms are rated as the worst problem by patients. Before day 2, antibiotics will have little chance to provide benefit, and after day 4, although some symptoms remain moderately bad or worse, on average, the mean diary scores for all symptoms are rated less than a moderately bad problem.[17]

New or worsening symptoms. This was defined as a return to the physician with worsening symptoms, new symptoms, new signs, or illness requiring admission to hospital within 4 weeks after the first consultation, determined from a review of the notes. This definition has been found useful and workable in previous studies of respiratory tract infection in the community.[18] Since so few patients required hospital admission, this outcome effectively represents symptom control.

Sample size calculation

Separating participants into two age bands < and ≥60 years, using the NQuery sample size program to detect a difference between age groups, it was calculated that 586 people were needed per age band to detect a 7.5% change to the deterioration of illness (15% versus 7.5%, 80% power, α = 0.05, 95% follow-up), and 544 were needed per age band to detect a chance of 0.33 standard deviations for the other two outcomes (80% power, α 0.01, 80% follow-up). The subgroups of interest in this study are of a similar magnitude to this (ranging from 409 in the group of those with green phlegm, to 817 in the group of those with longer duration of prior illness). A variety of abnormal lung signs were recorded: wheeze 305 (14%), rhonchi 281 (14%), crackles 126 (6%), and diminished vesicular breathing 256 (12%). No formal guidance was issued regarding characterisation of abnormal signs, and in a previous observational study in the same networks, variation in labelling of clinical signs between networks was evident.[19] Individual signs lacked power for subgroup analysis, so it was decided to combine abnormal physical findings into a new subgroup; 'abnormal signs' of similar magnitude to the other subgroups examined, 692 (34%). Since those with a clinical diagnosis of pneumonia were not included in the randomised study, these abnormal signs should be considered 'non-diagnostic of pneumonia'

Analysis

No interim analysis was performed, and all analyses were performed blind to group allocation, using Stata (version 11). Subgroup analyses were specified in advance. Analysis used linear regression models controlling for the severity of baseline symptoms: Cox regression for the duration of symptoms allowing for censoring; simple linear regression for symptom severity; and logistic regression for deterioration of illness. The interaction between a particular subgroup (for example, smokers) and the intervention (in this case antibiotics) concerns the difference in effectiveness (of antibiotics) in those in that particular subgroup (smokers), compared to those who are not (non-smokers). The interaction term is the variable introduced into the statistical model to allow estimation of the size of that difference. The effect size estimates shown in the tables relate to the prespecified subgroups of interest.

RESULTS

Participants

In total, 2061 participants were recruited between 2007 and 2010 and 595 (28%) of the trial population were aged ≥60 years, 310 (15%) had chronic lung disease (asthma or COPD). Deterioration of illness (or no deterioration) was documented in 98%, of whom 18% (356/2027) experienced deterioration; the vast majority of these represent reconsultation with new or worsening symptoms and only three patients required hospital admission (two from the control group and one from the intervention group) in the month following recruitment. Symptom severity and illness duration were documented in 87% and 88% respectively. The groups were well balanced at baseline.

Subgroup analysis for the three outcomes

No pre-specified subgroups were identified that were significantly more likely to benefit for the duration of symptoms rated

Table 1. Resolution of symptoms rated moderately bad or worse in amoxicillin versus placebo group

	Median time to resolution of symptoms rated moderately bad (IQR)		Interaction term[a]		Hazard ratio for subgroup[a]	
	Amoxicillin	Placebo	(95% CI)	*P*-value	(95% CI)	*P*-value
Whole cohort (*n* = 1799)	6 (3–11)	7 (4–14)			1.06 (0.98 to 1.18)	0.229
Green sputum (*n* = 346)	6 (3–10)	8 (5–14)	1.28 (0.99 to 1.65)	0.059	1.31 (1.05 to 1.65)	0.019
Current smoker (*n* = 487)	6 (4–10)	7 (4–14)	1.20 (0.95 to 1.51)	0.121	1.23 (1.01 to 1.50)	0.044
Significant past history[b] (*n* = 440)	6 (4–16)	8 (5–15)	0.98 (0.78 to 1.25)	0.914	1.06 (0.86 to 1.31)	0.581
Prior duration of illness >7 days (*n* = 715)	6 (4–15)	7 (3–14)	0.81[c] (0.66 to 0.99)	0.040	0.93 (0.79 to 1.09)	0.375
Fever at baseline (*n* = 608)	7 (4–14)	7 (4–11)	0.97 (0.78 to 1.20)	0.783	1.04 (0.88 to 1.25)	0.599
Minor chest signs (*n* = 692)	6 (4–14)	6 (4–15)	0.98 (0.79 to 1.21)	0.832	1.05 (0.88 to 1.24)	0.598

IQR = interquartile range. [a]Estimates controlled for baseline symptom severity. [b]Lung disease, heart disease, diabetes, or hospital admission. [c]The apparent anomaly here is that the proportional hazards assumption of hazards being constant over time was violated: the interaction term suggests a slower resolution in those with longer prior duration, whereas the median time to resolution suggests the opposite. The Kaplan–Meier survival curves cross, so although the median suggests a shorter duration, those receiving antibiotics have a group taking longer to resolve (90% of the placebo group recover by 24 days but it takes 28 days for 90% of the antibiotic group to recover).

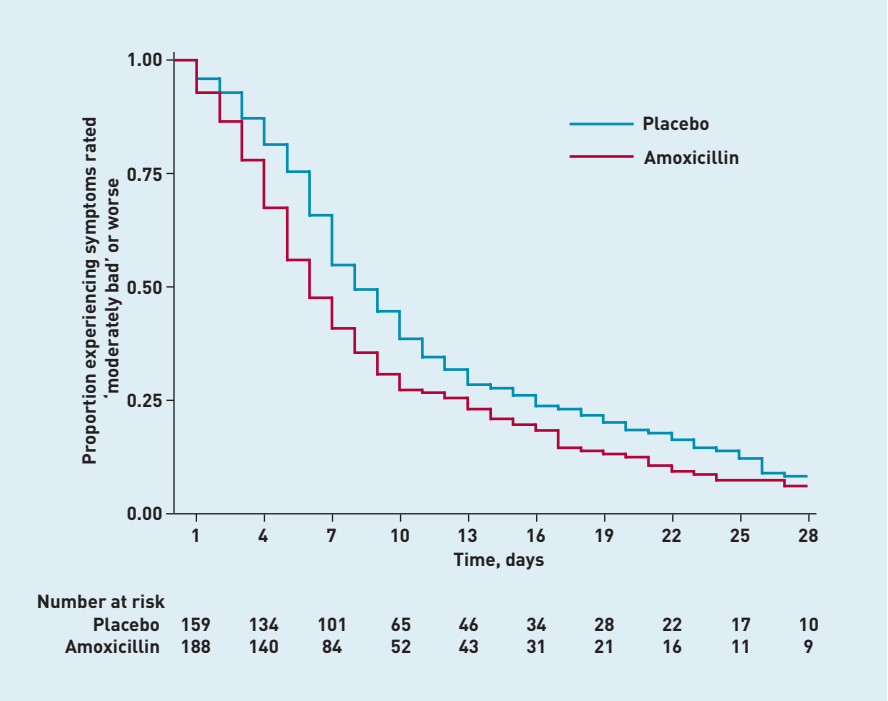

Figure 1. Kaplan–Meier survival curve for the duration of symptoms rated moderately bad or worse in patients with green sputum.

moderately bad or worse (Table 1). For those with green sputum, the interaction term was of borderline significance (interaction term 1.28; $P = 0.059$; hazard ratio in the subgroup [HR] = 1.31 [95% confidence interval {CI} = 1.05 to 1.65]; $P = 0.019$). A Kaplan–Meier survival curve is shown for those with green sputum (Figure 1). Although a separation of the survival curves may be seen, there is a modest impact on the median and interquartile range of symptom duration. Although the interaction term for those with a longer prior duration of illness is significant the effect is seen in the group with <7 days prior duration who experience a shortened duration of illness if they are given antibiotics (HR 1.18 [95% CI = 1.03 to 1.34; $P = 0.014$]).

For the symptom severity on days 2–4 (Table 2), those with a history of significant comorbidities (lung disease, heart disease, diabetes, or prior hospital admission) experienced a significantly greater reduction in symptom severity between days 2 and 4 than those without a past history (interaction term –0.28, $P = 0.003$; estimated effect of antibiotics among those with a past history –0.28 [95% CI = –0.44 to –0.11], $P = 0.001$). The significant interaction term for smoking relates to non-smokers: mean severity score: –0.12 (95% CI = –0.22 to –0.03; $P = 0.008$) and for duration of illness to those with shorter prior duration: mean severity score –0.16 (95% CI = –0.27 to –0.06; $P = 0.003$), although the differences were modest.

No subgroups were identified that were significantly more likely to develop new or worsening symptoms (Table 3). For those with abnormal lung signs, no benefit of antibiotics was seen in any of the three outcomes examined.

Table 2. Mean symptom severity score on days 2–4 after consultation, in amoxicillin versus placebo group

	Amoxicillin	Placebo	Interaction term[a] (95% CI)	*P*-value	Difference for subgroup[a] (95% CI)	*P*-value
Whole cohort (*n* = 1789)	1.62 (0.84)	1.69 (0.84)			–0.07 (–0.15 to 0.01)	0.074
Green sputum (*n* = 343)	1.79 (0.87)	1.91 (0.87)	–0.06 (–0.29 to 0.11)	0.398	–0.12 (–0.31 to 0.06)	0.196
Current smoker (*n* = 483)	1.85 (0.84)	1.77 (0.84)	0.19 (0.02 to 0.37)	0.029	0.07 (–0.07 to 0.23)	0.314
Significant past history[b] (*n* = 438)	1.63 (0.87)	1.90 (0.87)	–0.28 (–0.46 to –0.09)	0.003	–0.28 (–0.44 to –0.11)	0.001
Prior duration of illness >7 days (*n* = 711)	1.53 (0.77)	1.46 (0.77)	0.22 (0.06 to 0.38)	0.008	0.07 (–0.05 to 0.18)	0.253
Fever at baseline (*n* = 607)	1.94 (0.92)	2.02 (0.92)	–0.02 (–0.19 to 0.14)	0.799	–0.08 (–0.23 to 0.06)	0.262
Minor chest signs (*n* = 692)	1.81 (0.89)	1.89 (0.89)	–0.03 (–0.17 to 0.17)	0.791	–0.08 (–0.21 to 0.06)	0.288

[a]Estimates controlled for baseline symptom severity. [b]Lung disease, heart disease, diabetes, or hospital admission.

Table 3. Worsening of illness according to subgroup in amoxicillin versus placebo group

	Amoxicillin	Placebo	Interaction term[a] (95% CI)	*P*-value	Odds ratio for subgroup[a] (95% CI)	*P*-value
Whole cohort	162/1021	194/1006			0.79 (0.63 to 0.99)	0.043
Green sputum	40/221	43/185	0.93 (0.53 to 1.61)	0.787	0.73 (0.45 to 1.18)	0.202
Current smoker	47/304	45/269	1.21 (0.72 to 2.03)	0.482	0.91 (0.58,1.42)	0.680
Significant past history[b]	44/257	47/243	1.11 (0.65 to 1.88)	0.692	0.86 (0.55 to 1.36)	0.520
Prior duration of illness >7 days	70/411	74/390	1.16 (0.73 to 1.86)	0.528	0.88 (0.61 to 1.26)	0.474
Fever at baseline	59/345	70/347	1.05 (0.65 to 1.69)	0.844	0.82 (0.56 to 1.20)	0.300
Minor chest signs	57/345	70/334	0.92 (0.57 to 1.49)	0.740	0.75 (0.51 to 1.10)	0.139

[a]Estimates controlled for baseline symptom severity. [b]Lung disease, heart disease, diabetes, or hospital admission.

Funding

Funding was from the European Commission Framework Programme 6 (LSHM-CT-2005-518226). Eudract-CT 2007-001586-15 UKCRN Portfolio ID 4175 ISRCTN52261229 FWO G.0274.08N. The researchers are independent of all funders. The work in the UK was also supported by the National Institute for Health Research. In Barcelona, the work was supported by: 2009 SGR 911, Ciber de Enfermedades Respiratorias (Ciberes CB06/06/0028), the Ciberes is an initative of the ISCIII. In Flanders (Belgium), this work was supported by the Research Foundation — Flanders (FWO; G.0274.08N).

Ethical approval

Ethical approval for the UK was granted by Southampton and South West Hampshire Local Research Ethics Committee (B) (ref. 07/H0504/104). Competent authority approval for the UK was granted by the Medicines and Healthcare Products Regulatory Agency. The research sites outside of the UK also obtained ethical and competent authority approval from their local organisations. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and asked for informed consent.

Competing interests

The authors have declared no competing interests.

Acknowledgements

Key members of the GRACE consortium trial team whose hard work has made this possible are: Niels Adriaenssens, Zuzana Bielicka, Pascale Bruno, Jo Coast, Patricia Fernandez, Iris Hering, Anna Kowalczyk, Christina Lannering, Marieke Lemiengre, Katherine Loens, Christine Lammens, Greet Ieven , Bo-Eric Malmvall, Magdalena Muras, Nuria Sanchez Romano, Matteu Serra Prat, Igor Svab, Richard Smith, Jackie Swain, Paolo Tarsia, Frank Leus, Robert Veen, and Tricia Worby. We are very grateful to all the clinicians and patients who consented to be part of GRACE, without whom this study would simply not have been possible, and the independent GRACE trial steering committee for their help and suggestions (Patrick Bindels, Gordon Taylor, and Mark Woodhead).

Discuss this article

Contribute and read comments about this article: **www.bjgp.org/letters**

DISCUSSION

Summary

To the authors' knowledge, this is the largest multicentre randomised placebo controlled trial of antibiotics for acute uncomplicated LRTI and the first to provide robust estimates of benefit in common subgroups. It found no clear evidence of clinically meaningful selective benefit from antibiotics among key clinical subgroups of patients with uncomplicated LRTI where prescribing is highest.

Strengths and limitations

The findings are made relevant to everyday practice by the broad and pragmatic diagnostic entry criteria in the absence of an agreed definition for uncomplicated LRTI,[8] and by recruiting from multiple networks and countries. These inclusion criteria are consistent with recent pragmatic trials, large cohorts, and observational studies,[1,20–22] and with a recent consensus exercise.[23] It is unlikely that poor adherence diminished efficacy, since more than 90% of patients in both groups reported taking study medication by day 5 and data from observational studies suggest antibiotic choice is also unlikely to affect outcome.[2] There is a risk of type 1 error (false-positive result) with multiple comparisons in subgroups and so results should be treated with some caution; although the majority of the subgroups were identified in advance prior to the main analysis, an additional analysis was added at the request of the reviewers. In each instance, a positive result in a subgroup was seen in only one of the outcomes analysed, so it is feasible these findings arose by chance. Although a large trial, the study was not powered to detect rare but serious complications, such as empyema and hospital admission.

Comparison with existing literature

This study supports, to some extent, the approach taken in current guidelines, in that those with a prior history of significant comorbidity (lung disease, heart disease, diabetes, or hospital admission) appear to derive modest symptom benefit from antibiotics (a reduction of 0.28 in symptom score on day 2–4, which approximates to a 15% reduction in severity, or three people in 10 rating their symptoms a slight problem rather than a moderately bad problem). However, there was no other benefit in terms of resolution of symptoms rated moderately bad or worse, or worsening of symptoms in this group. In the absence of other benefits, the positive finding may be of limited clinical relevance. Any benefit needs to be balanced against the likely harms from treatment (a number needed to harm of around 20 for rash, nausea, or diarrhoea).[9]

Those with green sputum experienced a small but significant reduction in the duration of moderately bad symptoms but no change in symptom severity after 2–4 days, or likelihood of symptom deterioration. The interaction term was of borderline significance, so this result should be treated with some caution. This finding provides some evidence to back up GPs' tendency to prescribe for this group.[11,24] Although statistically significant, the confidence intervals were wide, and in the absence of benefit in other outcomes, the balance between benefit and harm is likely to be marginal and only a modest reduction in the median or interquartile range of symptom severity was observed. This finding must also be put in context with the observational evidence, which showed no benefit for those with coloured sputum.[11] No evidence was found to support greater prescribing in those who currently smoke,[25] and, if anything, non-smokers appear more likely to benefit. No evidence of benefit was found in those with abnormal chest signs (not diagnostic of pneumonia). Since crepitations and reduced breath sounds featured in the diagnostic model for pneumonia,[26] these were also examined as a separate (but small) subgroup (354/2061 [17%]) and the interaction terms were not significant for each of the outcomes. An unanticipated finding was that those with shorter duration of prior illness appeared to derive modest benefit in terms or duration of moderately bad symptoms and symptom severity, but this was not a prespecified subgroup. However this finding is consistent with recent evidence in acute sore throat in which short prior duration of illness was a predictor of streptococcal infection[27] and subsequent benefit from antibiotics.[28]

Given that a small number of patients with LRTIs may benefit from antibiotic treatment, it is unlikely that they can easily be identified from features of the history and clinical examination in primary care.

Implications for practice

A statistically significant reduction in symptom severity between days 2 and 4 was observed in those with pre-existing comorbidities; however, there was no benefit for duration of moderately bad symptoms or worsening of illness. Those with green sputum possibly experienced a small reduction in the duration of moderately bad symptoms. The modest short-term benefits are of questionable clinical significance and must be balanced against the side-effects and the longer-term harm of fostering antibiotic resistance.

REFERENCES

1. Butler CC, Hood K, Verheij T, *et al.* Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009; **338:** b2242.
2. Butler CC, Hood K, Kelly MJ, *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 Chemother* 2010; **65(11):** 2472–2478.
3. Petersen I, Johnson AM, Islam A, *et al.* Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007; **335(7627):** 982.
4. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, *et al.* Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J Antimicrob Chemother* 2004; **54(6):** 1116–1121.
5. Gonzales R, Bartlett JG, Besser RE, *et al.* Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: background. *Ann Emerg Med* 2001; **37(6):** 720–727.
6. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; **26(6):** 1138–1180.
7. National Institute for Health and Care Excellence. *Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care.* London: NICE, 2011.
8. Smith SM, Fahey T, Smucny J, Becker L. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2009; **(4):** CD000245.
9. Little P, Stuart B, Moore M, *et al.* Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13(2):** 123–129.
10. Brookes-Howell L, Hood K, Cooper L, *et al.* Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. *BMJ Open* 2012; **2(3):** pii: e000795.
11. Butler CC, Kelly MJ, Hood K, *et al.* Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection. *Eur Respir J* 2011; **38(1):** 119–125.
12. Coenen S, Michiels B, van Royen P, *et al.* Antibiotics for coughing in general practice: a questionnaire study to quantify and condense the reasons for prescribing. *BMC Fam Pract* 2002; **3:** 16.
13. Brookes-Howell L, Hood K, Cooper L, *et al.* Understanding variation in primary medical care: a nine-country qualitative study of clinicians' accounts of the non-clinical factors that shape antibiotic prescribing decisions for lower respiratory tract infection. *BMJ Open* 2012; **2(4):** pii: e000796.
14. Coenen S, Michiels B, Renard D, *et al.* Antibiotic prescribing for acute cough: the effect of perceived patient demand. *Br J Gen Pract* 2006; **56(524):** 183–190.
15. British Thoracic Society Guidelines for the management of Community Acquired Pneumonia. *Thorax* 2001; **56(suppl IV):** 1–64.
16. Watson L, Little P, Moore M, *et al.* Validation study of a diary for use in acute lower respiratory tract infection. *Fam Pract* 2001; **18(5):** 553–554.
17. Little P, Rumsby K, Kelly J, *et al.* Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *JAMA* 2005; **293(24):** 3029–3035.
18. Hay AD, Fahey T, Peters TJ, Wilson A. Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study. *Br J Gen Pract* 2004; **54(498):** 9–14.
19. Francis NA, Melbye H, Kelly MJ, *et al.* 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. *Eur J Gen Pract* 2013; **19(2):** 77–84.
20. Macfarlane J, Holmes W, Gard P, *et al.* Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001; **56(2):** 109–114.
21. Macfarlane JT, Colville A, Guion A, *et al.* Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* 1993; **341(8844):** 511–514.
22. Coenen S, Van RP, Michiels B, Denekens J. Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. *J Antimicrob Chemother* 2004; **54(3):** 661–672.
23. Greene G, Hood K, Little P, *et al.* Towards clinical definitions of lower respiratory tract infection (LRTI) for research and primary care practice in Europe: an international consensus study. *Prim Care Respir J* 2011; **20(3):** 299–306.
24. Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. *Br J Gen Pract* 2001; **51(464):** 177–181.
25. Stanton N, Hood K, Kelly MJ, *et al.* Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit? An observational study in 13 European countries. *Eur Respir J* 2010; **35(4):** 761–767.
26. van Vugt SF, Broekhuizen BD, Lammens C, *et al.* 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. *BMJ* 2013; **346:** f2450.
27. Little P, Moore M, Hobbs FDR, *et al.* PRImary care Streptococcal Management (PRISM) study: identifying clinical variables associated with Lancefield group A beta-haemolytic streptococci and Lancefield non-Group A streptococcal throat infections from two cohorts of patients presenting with an acute sore throat. *BMJ Open* 2013; **3:** e003943 doi:10.1136/bmjopen-2013-003943.
28. Little P, Hobbs FDR, Moore M, *et al.* Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ* 2013; **347:** f5806.