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Antibiotic prescribing for adults with acute cough/lower respiratory tract infection: congruence with guidelines

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ABSTRACT: European guidelines for treating acute cough/lower respiratory tract infection (LRTI) aim to reduce nonevidence-based variation in prescribing, and better target and increase the use of first-line antibiotics. However, their application in primary care is unknown. We explored congruence of both antibiotic prescribing and antibiotic choice with European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for managing LRTI.

The present study was an analysis of prospective observational data from patients presenting to primary care with acute cough/LRTI. Clinicians recorded symptoms on presentation, and their examination and management. Patients were followed up with self-complete diaries.

1,776 (52.7%) patients were prescribed antibiotics. Given patients' clinical presentation, clinicians could have justified an antibiotic prescription for 1,915 (71.2%) patients according to the ERS/ESCMID guidelines. 761 (42.8%) of those who were prescribed antibiotics received a first-choice antibiotic (*i.e.* tetracycline or amoxicillin). Ciprofloxacin was prescribed for 37 (2.1%) and cephalosporins for 117 (6.6%).

A lack of specificity in definitions in the ERS/ESCMID guidelines could have enabled clinicians to justify a higher rate of antibiotic prescription. More studies are needed to produce specific clinical definitions and indications for treatment. First-choice antibiotics were prescribed to the minority of patients who received an antibiotic prescription.

KEYWORDS: Antibiotic resistance, clinical epidemiology, infections, lower respiratory tract infections, primary care

European guidelines have been developed and promoted to reduce nonevidence-based and unhelpful variation in care. Guidelines for managing suspected infection should help clinicians better target antibiotic prescribing to those most likely to benefit and increase the proportion of prescribing of first-line agents in the hope that this will result in more effective care, reduced risk to patients and help contain antibiotic resistance.

In collaboration with the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Respiratory Society (ERS) published guidelines on when and which antibiotics should be prescribed in patients presenting with lower respiratory tract infection (LRTI) in primary care [1]. The guideline developers faced challenges arising from gaps in the supporting evidence base and, hence, some recommendations were based on consensus and compromise rather than empirical evidence. It is not known to what extent actual prescribing practice across Europe is congruent with such key guidelines in primary care.

The prospective, observational GRACE (Genomics to Combat Resistance Against Antibiotics in Community-Acquired LRTI in Europe; www.grace-lrti.org) 01 study of the presentation, management and outcome of acute cough in primary care identified considerable variation in antibiotic prescribing for acute cough in Europe that could not be explained by variation in clinical presentation, and which was not associated with clinically important differences in recovery [2, 3]. An important reason why this study focused on adults

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is because the greatest number of antibiotic prescription for LRTI is for this age group [4].

Here, we explore the extent to which the level of antibiotic prescribing and actual antibiotic choice for treating acute cough was congruent with the recommendations in ERS/ESCMID guidelines.

MATERIALS AND METHODS

Participants

Eligible patients were: aged $\geqslant$18 yrs; were consulting with an illness where an acute or worsened cough was the main or dominant symptom, or had a clinical presentation that suggested a LRTI, with a duration of $\leqslant$28 days; consulting for the first time within this illness episode; seen within normal consulting hours; had not previously participated in the study; were able to fill out study materials; had provided written informed consent; and were considered immunocompetent.

Participating general practitioners (GPs) were asked to recruit consecutive eligible patients from October to November 2006 and late January to March 2007.

Study design

The GRACE study was a prospective observational study in 14 primary care research networks in 13 European countries [2, 3, 5, 6].

Setting

The GRACE Network of Excellence recruited 14 primary care research networks (based in the cities of: Cardiff, UK; Southampton, UK; Utrecht, the Netherlands; Barcelona, Spain; Mataro, Spain; Rotenberg, Germany; Balatonfured, Hungary; Antwerp, Belgium; Lodz, Poland; Milan, Italy; Jönköping, Sweden; Tromsø, Norway; Helsinki, Finland; and Bratislava, Slovakia) in 13 countries (Wales, England, the Netherlands, Spain (two networks), Germany, Hungary, Belgium, Poland, Italy, Sweden, Norway, Finland and Slovakia) as previously described [3].

Data sources/measurements

Clinicians (GPs and nurse practitioners) recorded aspects of patients' history, symptoms, comorbidities (diabetes, chronic lung disease and cardiovascular disease), and clinical findings and their management, in particular antibiotic prescription, on a case report form (CRF). If an antibiotic was prescribed, the clinician was then asked to record the name of the antibiotic. Antibiotics were subsequently categorised into classes, informed by British National Formulary subcategories [7].

Clinicians recorded the presence or absence of (among others) cough, shortness of breath, phlegm production and colour, and fever during illness, and then rated the severity of symptoms on a four-category scale.

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 seven-point scale from ''normal/not affected'' to ''as bad as it can be''. The diary also asked how many days they were unwell before they saw their GP or nurse for their cough.

Variables

The ERS/ESCMID guidelines list six patient subgroups where antibiotics should be considered: those with suspected or definite pneumonia; those with selected exacerbations of chronic obstructive pulmonary disease (COPD); those aged 75 yrs with fever; those with cardiac failure; those with insulin-dependent diabetes mellitus; and those with a serious neurological disorder. We proxied these subgroups using CRFs and diary data (supplementary material table 1).

Pneumonia

The ERS/ESCMID guidelines define suspected or definite pneumonia as an acute cough and one of: 1) new focal chest signs; 2) dyspnoea; 3) tachypnoea; and 4) fever lasting 4 days. This was proxied by having an acute cough and one of: 1) diminished vesicular breathing, crackles or rhonchi; 2) shortness of breath; 3) tachypnoea was modelled by respiratory rate $>$20 breaths·min^{-1} [8, 9]; and 4) fever (temperature $>$37.8°C) in patients who had waited $\geqslant$4 days before consulting their GP or nurse.

COPD

The guidelines state that selected exacerbations of COPD where antibiotics are indicated require a diagnosis of COPD and all three of: 1) increased dyspnoea; 2) increased sputum volume; and 3) increased sputum purulence or a diagnosis of severe COPD (*i.e.* patients with a severe exacerbation that requires invasive or noninvasive mechanical ventilation). We proxied this by selecting those patients in our study with COPD and all of: 1) shortness of breath; 2) phlegm production; 3) phlegm colour yellow, green or bloodstained, or with an oxygen saturation measured by pulse oximetry (S_pO_2) $<$90%, as this is a cut-off point used in the Pneumonia Severity Index [1, 10].

Fever in the elderly

CRF data on patients' age and fever (which we defined as body temperature $>$37.8°C) was recorded using a disposable thermometer (TempaDot; 3M Health Care, Loughborough, UK).

Cardiac failure

Cardiac failure was considered present if a clinician recorded a diagnosis of heart failure.

Insulin-dependent diabetes

Insulin-dependent diabetes mellitus was considered present if a clinician recorded a diagnosis of diabetes and the patient was taking insulin regularly.

Serious neurological disorders

No information was collected regarding serious neurological disorders.

Antibiotics

The guidelines recommend tetracycline and amoxicillin as ''preferred'' antibiotics. In cases of hypersensitivity, macrolides are recommended as an ''alternative'' antibiotic. When clinically relevant bacterial resistance rates against all first-choice agents exist, levofloxacin and moxifloxacin are also recommended as an ''alternative''. Amoxicillin–clavulanate is also included as a suitable ''alternative'' antibiotic.

First, we assessed ERS/ESCMID guideline congruence regarding the decision whether or not to prescribe antibiotics for acute cough/LRTI (antibiotic prescribing analysis). We distinguished between ''congruent prescribing'', ''congruent nonprescribing'', ''noncongruent prescribing'' and ''noncongruent nonprescribing''. Secondly, we assessed the proportion of guideline congruence regarding the antibiotic choice in those patients who were prescribed an antibiotic (antibiotic choice analysis).

Statistical methods

Descriptive statistics are presented for antibiotic prescribing and antibiotic type in comparison with the guidelines. These are also presented by network to explore variation in congruence across Europe.

RESULTS

Participants

387 practitioners recruited 3,402 patients. Six networks included ⩾270 patients and all included >100. Four patients were later found to be ineligible and were therefore excluded from further analysis. CRFs were completed for 3,368 (99%), which were included in the antibiotic choice analysis. Diary data was obtained from 2,714 (80%) patients. 2,690 (79%) completed both the CRF and diary, and were included in the antibiotic prescribing analysis. Patients not included in the latter analysis were younger and less frequently prescribed antibiotics, but were similar to included patients in terms of sex, clinical presentation and comorbidities.

Descriptive data

The participants had a median age of 48 yrs (interquartile range (IQR) 35–60 yrs). 36.2% were male, 5.8% had COPD, 1.7% had heart failure and 4.7% had diabetes. As for the symptoms used to proxy the ERS/ESCMID guidelines, 99.8% had cough, 50.7% had shortness of breath, 77.1% had phlegm production and 46.5% had purulent sputum. Patients were unwell for a median of 5 days (IQR 3–8 days) before consulting their GP. The median temperature was 36.8°C (IQR 36.4–37.2°C).

Main results

Antibiotic prescribing

An antibiotic was prescribed to 1,776 (52.7%) out of 3,368 GRACE patients with completed CRFs. We could only include 2,690 patients in the rest of the antibiotic prescribing analysis, as both CRF and patient-completed diary questionnaires were required to obtain all the proxy data. Of these 2,690 patients, just over half (n=1,464; 54.4%) were prescribed an antibiotic (table 1). Our exploratory analysis suggests that clinicians could have justified an antibiotic prescription in 71.2% (n=1,915) by a literal reading of the ERS/ESCMID guidelines.

In 1,745 (64.9%) patients, the decision of whether or not to prescribe was congruent with the ERS/ESCMID guideline (table 1). Figure 1 shows the distribution of antibiotic types observed in each network. We observed 45.2% congruent prescribing, 19.6% congruent nonprescribing, 9.2% noncongruent prescribing and 25.9% noncongruent nonprescribing (table 1). Table 2 provides information on the percentages of each type of prescribing split by network, and this is graphed in Figure 2.

An estimated 70.8% of patients could have been considered to have suspected or definite pneumonia according to our exploratory analysis; other reasons were less frequent (2.9% selected exacerbations of COPD; 0.4% aged 75 yrs with fever; 1.7% cardiac failure; 0.9% insulin-dependent diabetes mellitus; no data for serious neurological disorder). However, clinicians reported pneumonia as their working diagnosis in only 4.3% of cases (other working diagnoses included LRTI (44.8%), upper respiratory tract infection (25.9%), general viral infection (10.5%), nonspecific respiratory infection (3.4%), cough (3.3%), asthma (3.2%), COPD (3%), other nonspecific (0.6%) and hyperresponsiveness (0.4%)). In order to investigate this further,

TABLE 1 Contingency table of ERS/ESCMID guideline-recommended antibiotic to be considered *versus* observed antibiotic prescribed

	Antibiotic to be considered		Total
	No	Yes	
Antibiotic prescribed			
No	528 (19.6)	698 (25.9)	1226 (45.6)
Yes	247 (9.2)	1217 (45.2)	1464 (54.4)
Total	775 (28.8)	1915 (71.2)	2690 (100.0)

Data are presented as n (%). ERS: European Respiratory Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases.

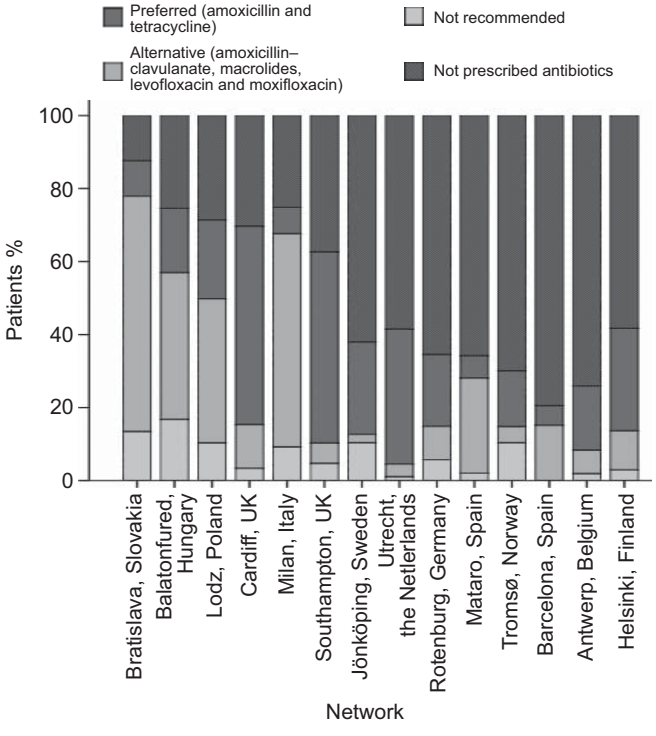

FIGURE 1. Stacked bar chart of the percentages of antibiotics grouped according to European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guideline recommendations prescribed by network.

TABLE 2 Proportions of antibiotic choice congruence to ERS/ESCMID guidelines for lower respiratory tract infection by network

	Congruent prescribing	Congruent nonprescribing	Noncongruent prescribing	Noncongruent nonprescribing	Total n
Bratislava, Slovakia	177 (59.2)	11 (3.7)	85 (28.4)	26 (8.7)	299
Balatonfured, Hungary	237 (74.1)	7 (2.2)	2 (0.6)	74 (23.1)	320
Lodz, Poland	120 (54.3)	36 (16.3)	40 (18.1)	25 (11.3)	221
Cardiff, UK	116 (64.1)	16 (8.8)	14 (7.7)	35 (19.3)	181
Milan, Italy	95 (62.1)	22 (14.4)	26 (17.0)	10 (6.5)	153
Southampton, UK	86 (51.2)	26 (15.5)	19 (11.3)	37 (22.0)	168
Jönköping, Sweden	75 (33.8)	59 (26.6)	8 (3.6)	80 (36.0)	222
Utrecht, the Netherlands	77 (39.5)	43 (22.1)	5 (2.6)	70 (35.9)	195
Rotenburg, Germany	49 (27.1)	42 (23.2)	12 (6.6)	78 (43.1)	181
Mataro, Spain	47 (26.3)	75 (41.9)	15 (8.4)	42 (23.5)	179
Tromsø, Norway	42 (28.4)	24 (16.2)	3 (2.0)	79 (53.4)	148
Barcelona, Spain	19 (11.2)	105 (62.1)	12 (7.1)	33 (19.5)	169
Antwerp, Belgium	41 (25.0)	40 (24.4)	3 (1.8)	80 (48.8)	164
Helsinki, Finland	36 (40.0)	22 (24.4)	3 (3.3)	29 (32.2)	90
Total	1217 (45.2)	528 (19.6)	247 (9.2)	698 (25.9)	2690

Data are presented as n (%), unless otherwise stated. ERS: European Respiratory Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases.

a sensitivity analysis was performed so that the guideline definition of suspected or definite pneumonia was modified from acute cough and one of 1) new focal chest signs, 2) dyspnoea, 3) tachypnoea and 4) fever lasting 4 days, to acute cough and two of the aforementioned symptoms. Under these new conditions, the percentage with suspected or definite pneumonia reduced to 27.8% and the overall percentage where an antibiotic could have been justified reduced from 71.2% to 29.7%. Increasing the number of symptoms required to three reduced the percentage with suspected or definite pneumonia

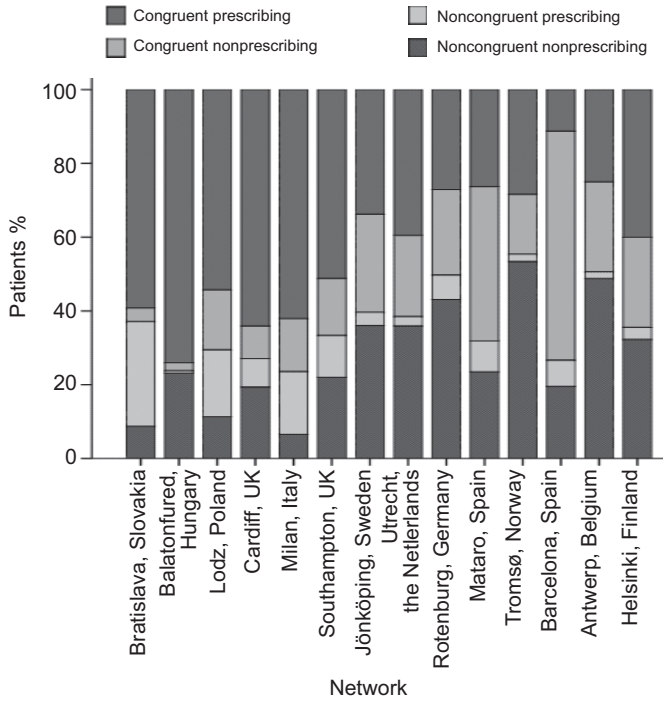

FIGURE 2. Stacked bar chart of the percentages of antibiotic prescribing decision congruence to European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guideline recommendations by network.

TABLE 3 Proportions of antibiotic choice congruence to ERS/ESCMID guidelines for lower respiratory tract infection by network

	Preferred#	Alternative¶	Not recommended	Total n
Bratislava, Slovakia	29 (11.1)	193 (73.7)	40 (15.3)	262
Balatonfured, Hungary	57 (23.7)	130 (53.9)	54 (22.4)	241
Lodz, Poland	65 (30.2)	119 (55.3)	31 (14.4)	215
Cardiff, UK	163 (78.0)	36 (17.2)	10 (4.8)	209
Milan, Italy	15 (9.7)	121 (78.1)	19 (12.3)	155
Southampton, UK	112 (83.6)	12 (9.0)	10 (7.5)	134
Jönköping, Sweden	76 (66.7)	7 (6.1)	31 (27.2)	114
Utrecht, the Netherlands	74 (89.2)	7 (8.4)	2 (2.4)	83
Rotenburg, Germany	45 (57.0)	21 (26.6)	13 (16.5)	79
Mataro, Spain	12 (17.9)	51 (76.1)	4 (6.0)	67
Tromsø, Norway	31 (50.8)	9 (14.8)	21 (34.4)	61
Barcelona, Spain	15 (26.3)	42 (73.7)	0 (0.0)	57
Antwerp, Belgium	38 (67.9)	14 (25.0)	4 (7.1)	56
Helsinki, Finland	29 (67.4)	11 (25.6)	3 (7.0)	43
Total	761 (42.8)	773 (43.5)	242 (13.6)	1776

Data are presented as n (%), unless otherwise stated. ERS: European Respiratory Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases. #: amoxicillin and tetracycline; ¶: macrolides, amoxicillin–clavulanate, levofloxacillin and moxifloxacin.

TABLE 4 Contingency table of antibiotic choice and antibiotic prescribing decision congruence to ERS/ESCMID guidelines in prescribed patients with lower respiratory tract infection

	Antibiotic choice		Total
	Yes	No	
Antibiotic prescribing decision			
Yes	518 (35.4)	699 (47.7)	1217 (83.1)
No	76 (5.2)	171 (11.7)	247 (16.9)
Total	594 (40.6)	870 (59.4)	1464 (100.0)

Data are presented as n (%). ERS: European Respiratory Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases.

to 3.1% and the percentage to be considered for antibiotic prescribing was reduced to 8.0%.

An additional sensitivity analysis was carried out on chest signs, as details on new focal signs were not recorded, as defined in the guidelines. Excluding chest signs completely reduced the proportion of patients for whom an antibiotic could have been justified from 71.2% to 53.6%.

Antibiotic choice

Of those prescribed an antibiotic, the first-choice antibiotics tetracycline or amoxicillin were prescribed for 761 (42.8%), 773 (43.5%) received a prescription for an alternative antibiotic and 242 (13.6%) received an antibiotic not recommended by the ERS/ESCMID guidelines (table 3), including 37 (2.1%) receiving ciprofloxacin and 117 (6.6%) receiving cephalosporins. The majority of the patients in eight out of the 14 networks received a first-choice antibiotic. In Utrecht, 89.2% of those prescribed received a first-choice agent, compared with Milan where only 9.7% were prescribed amoxicillin or tetracycline.

In 518 (42.6%) out of 1,217 patients who were prescribed an antibiotic consistent with the ERS/ESCMID guidelines, the antibiotic choice was also congruent with the ERS/ESCMID guidelines (table 4). In the other patients prescribed an antibiotic (noncongruent prescribing), this proportion was 76 (30.8%) out of 247 patients.

DISCUSSION

Key results

Overall, an antibiotic was prescribed in 1,776 (52.7%) patients with acute cough/LRTI in this 13-country, prospective, observational primary care study. We estimated from exploratory analyses that clinicians, had they been so minded could have justified antibiotic prescribing for even larger numbers of patients (>70%) through a literal interpretation of ERS/ESCMID guidelines on the management of acute LRTI. Tromsø was the least congruent prescribing network, with 55.4% of antibiotic prescribing decisions not ERS/ESCMID guideline-congruent. This is largely accounted for by the patients not being prescribed an antibiotic when the guidelines could have justified an antibiotic prescription. However, this network prescribed antibiotics to a low proportion of patients and generally used narrow agents. This highlights caution that needs to be applied to interpreting this aspect of the analysis.

A first-choice antibiotic (according to the ERS/ESCMID guidelines) was prescribed to 761 (42.8%) patients; 773 (43.5%) received a recommended alternative antibiotic and 242 (13.6%) were prescribed an antibiotic that was not recommended by the guidelines. However, agents such as ciprofloxacin (2.1%) and cephalosporins (6.6%) were not widely used.

Strengths and limitations

The broad inclusion criteria allowed for patients with community-acquired LRTI presenting a range of symptoms to be analysed. We used the data that we collected to proxy criteria specified in the guidelines. This increased the chance of error in our prescribing analyses. For example, we did not collect data on new focal chest signs, so auscultation findings on the day of consultation were used instead. We do not know how many of these auscultation abnormalities were, in fact, new signs. However, in practice, many patients are seen by clinicians who would not know if abnormalities on auscultation were new or not. We did not ask clinicians to distinguish between focal and generalised abnormalities on auscultation. This could have led to an overestimation of those for whom a prescription could have been justified, as ERS/ESCMID guidelines consider antibiotics are indicated in the case of focal abnormalities. The sensitivity analysis showed that excluding patients with chest signs would still mean that an antibiotic could have been justified (on the basis of other findings) in the majority of patients. We were unable to identify patients with serious neurological disorder. Moreover, some measures (respiratory rate and S_{p,O_2}) used to assess symptoms were not performed on all patients in the study, as these examinations were performed at the discretion of the clinicians. Patients with diabetes mellitus taking insulin were considered equivalent to patients with insulin-dependent diabetes, but this may have included people with type II diabetes who were treated with insulin. Duration of fever was not recorded during presentation, hence we had to make the assumption that duration of illness >4 days prior to consultation implied fever >4 days, if fever was present at consultation. We are conscious that individual countries may have followed their own national guidelines and in some cases a Europe-wide guideline may not be appropriate.

Selection bias of both clinicians and patients may have affected the results. Given that research networks are likely to include practitioners who are more ''guideline aware'', the true rate of adherence to guidelines in primary care in Europe may be lower than described in this study. We asked clinicians to recruit sequential patients into the study, but as they were not able to keep logs of eligible patients, we do not know what proportion of eligible patients was recruited. It is possible that more patients were recruited at less busy times. Patients who were favourably disposed to clinicians may have been over-represented.

Interpretation

Achieving uptake of guidelines into everyday clinical care remains a challenge, with a recent study finding that some

clinicians consider antibiotic resistance to be generally unaffected by their practice and that some clinicians prescribe broad-spectrum antibiotics for some LRTI patients in order to give their patients the best chance of recovery and prevent hospital admissions [11]. Further research should generate a better understanding of suboptimal guideline uptake and identify opportunities for intervention development. Guidelines may also allow clinicians to justify antibiotic prescribing in more cases than intended, especially when definitions are broadly specified because of a suboptimal evidence base. Guideline developers face many challenges, including making treatment recommendations in the context of imperfect evidence. It must be acknowledged that while the guidelines suggested clinicians consider antibiotic treatment when certain signs or symptoms were present, they do not say that antibiotic treatment is justified in all patients with these symptoms. Moreover, the very broad definition of suspected pneumonia arose from a lack of evidence from rigorous diagnostic studies in this field [9, 12, 13].

Implications for practice and research

Previous research has identified both over- and under-prescribing of antibiotics for common infections in primary care [14, 15]. Over-prescribing risks unnecessarily exposing patients to risk of side-effects without achieving meaningfully more rapid recovery [16]. This also impacts on carriage of antibiotic-resistant organisms [17], risk of infection with resistant organisms [18], patient recovery and workload in general practice [19], and costs [20].

However, reduced prescribing at a general practice level has been associated with reductions in antibiotic resistance locally [21].

Under-prescribing may result in increased risk of pneumonia as identified in retrospective studies using routinely collected data form general practice [22, 23].

Our study has identified an opportunity to minimise nonevidence-based variation in antibiotic prescribing across Europe, despite the existence of a relevant European guideline [1]. Achieving an understanding of the reasons for suboptimal guideline adherence is an urgent prerequisite to intervention development aimed at improving practice. Antibiotic choice often varies from guideline recommendations and, in their present form, the ERS/ESCMID guidelines could be used to justify increased antibiotic prescribing if literally applied. Narrower definitions of suspected pneumonia may enhance future versions of this guideline. More diagnostic research in primary care is needed to enable this.

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STATEMENT OF INTEREST

Statements of interest for T. Verheij, A. Torres and T. Schaberg can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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