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Original Research

ANTIBIOTICS AND RESPIRATORY INFECTIONS

Antibiotic Prescribing and Outcomes of Lower Respiratory Tract Infection in UK Primary Care*

Christopher C. Winchester, DPhil; Tatiana V. Macfarlane, PhD; Mike Thomas, MBBS; and David Price, MB BChir

Background: **Lower respiratory tract infection (LRTI) is common in the community and may result in hospitalization or death. This observational study aimed to investigate the role of antibiotics in the management of LRTI in the primary care setting in the United Kingdom.**

Methods: **Patients receiving a first diagnosis of LRTI during 2004 and satisfying inclusion and data quality criteria were identified in the General Practice Research Database. Factors associated with respiratory infection-related hospital admissions and death in the 3 months following the initial diagnosis were identified using Cox proportional hazards regression.**

Results: **Antibiotic prescribing on the day of diagnosis was associated with a decreased rate of respiratory infection-related hospital admission (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.58 to 0.92), while antibiotic prescribing in the previous 7 days (HR, 1.92; 95% CI, 1.24 to 2.96) and prior referral or hospitalization (HR, 1.48; 95% CI, 1.20 to 1.83) were associated with an increased risk of hospital admission. Female sex (HR, 0.73; 95% CI, 0.64 to 0.84), allergic rhinitis (HR, 0.48; 95% CI, 0.27 to 0.83), influenza vaccination (HR, 0.75; 95% CI, 0.65 to 0.87), prior inhaled corticosteroid use (HR, 0.63; 95% CI, 0.52 to 0.76), and antibiotic prescription on the day of diagnosis (HR, 0.31; 95% CI, 0.26 to 0.37) were associated with decreased respiratory infection-related mortality, while a Charlson comorbidity index of ≥ 2 (HR, 2.24; 95% CI, 1.72 to 2.92), antibiotic prescription in the previous 7 days (HR, 1.56; 95% CI, 1.20 to 2.03), and frequent consultation (HR, 1.62; 95% CI, 1.09 to 2.40) were associated with increased mortality.**

Conclusions: **Antibiotic prescribing on the day of LRTI diagnosis was associated with reductions in hospital admissions and mortality related to respiratory infection. Antibiotics may help to prevent adverse outcomes for some patients with LRTI.** ***(CHEST 2009; 135:1163–1172)***

Abbreviations: BMI = body mass index; CI = confidence interval; GPRD = General Practice Research Database; HR = hazard ratio; ICS = inhaled corticosteroid; LRTI = lower respiratory tract infection; NHS = National Health Service; NTT = number needed to treat; PCP = primary care physician

Respiratory tract infection is a very common reason for consultation in primary care,[1] and patients present with a spectrum of disease ranging from minor self-limiting illnesses to potentially life-threatening infections. Community-acquired pneumonia accounts for between 5% and 12% of all cases of adult lower respiratory tract infection (LRTI) managed by primary care physicians (PCPs) in the community.[2] Although the presence of normal vital signs makes a diagnosis of pneumonia unlikely, a definitive diagnosis cannot be made clinically without a chest radiograph, which is not feasible in all cases.[2] Diagnosis is particularly problematic in the elderly and in patients with cardiac or respiratory comorbidity.[2] Most cases of pneumonia result from bacterial infection,[2] and antibiotic therapy remains the mainstay of pneumonia management.[2] The role of antibiotics in the management of the broaderpopulation of patients with LRTI is less clear.[3]

For editorial comment see page 1118

Substantial reductions in rates of consultation and antibiotic prescribing for LRTI have been observed in the past few years,[4–7] perhaps as a result of guidance aiming to curb antimicrobial resistance.[8,9] A study[10] of population-level data in England and Wales reported that decreasing winter antibiotic prescribing for LRTI during the second half of the 1990s was associated with a significant increase in excess winter pneumonia mortality. Similar trends have been seen in studies[11–13] of hospitalization rates for respiratory tract infection. Cross-sectional population studies,[11,14,15] however, have shown mixed results.

Studies based on data from populations are open to the "ecological fallacy," which notes that exposure and outcome in any one individual may not be linked.[16,17] Patient-level data from UK primary care[18] have shown that antibiotic prescribing for respiratory tract infection is associated with a significantly reduced risk of pneumonia. However, the impact of antibiotic prescribing on clinically meaningful outcomes (identified as a research priority by the International Primary Care Respiratory Group) remains unknown. The objective of this International Primary Care Respiratory Group-funded study was to investigate the association of antibiotic prescribing and other potential risk factors with hospital admissions and death related to respiratory infections in patients consulting a PCP for the treatment of an LRTI.

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This study is based in part on data from the Full Feature General Practice Research Database obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone. The original idea for the study and the protocol were formulated by Drs. Winchester, Thomas, and Price, with subsequent advice and statistical input from Dr. Macfarlane, who also performed the statistical analyses. Dr. Winchester drafted the manuscript, with extensive contributions and revision from all authors.

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Dr. Winchester is employed as a medical writer by Oxford PharmaGenesis Ltd. He and Oxford PharmaGenesis have received no industry funding for this research and are undertaking no industry-sponsored projects related to antibiotics or respiratory infection. Dr. Thomas received an honorarium for giving a lecture at an educational meeting arranged by Abbott Laboratories in 2007. Dr. Price is on the independent steering committee of a study looking at the treatment of lower respiratory tract infection in Europe sponsored by Bayer Healthcare; also, he chairs the Research Subcommittee of the International Primary Care Respiratory Group but was not involved in approving this study for funding. Dr. Macfarlane has reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Materials and Methods

Study Population

Patients receiving an LRTI diagnosis in 2004 were identified in the UK General Practice Research Database (GPRD). This primary care database contains demographic, diagnostic, treatment, and referral information on approximately 3 million patients who are registered with approximately 1,500 participating PCPs. This information is sent in a deidentified format to the Medicines and Healthcare Products Regulatory Agency and made available for use in research projects. The population covered by the GPRD is representative of the UK general population as a whole,[19,20] and the accuracy and completeness of data from the GPRD have been documented in several validation studies.[21–25] The GPRD has also been used successfully in studies of antibiotic prescribing and/or respiratory disease.[5,6,18,26–30]

Patients with an LRTI diagnosis during the study period (January 1 to December 31, 2004) were identified using Read codes for acute LRTI (including influenza, pneumonia, and acute bronchitis), as described in Appendix 1 of the online supplemental material. The population consisted of patients who, at the beginning of the study period, were enrolled with a PCP, had been participating in the GPRD for at least 1 year and were at least 1 year of age, to enable the collection of complete morbidity information in the year before the index date (*ie*, the first date in 2004 on which the PCP diagnosed an LRTI). Patients were excluded from the study if they had received a diagnosis of LRTI in the month before the index date (to exclude patients in prevalent cases who consulted in January 2004 for an LRTI first diagnosed in December 2003) or had obviously incorrect data (*eg*, a date of death preceding the index date or date of hospitalization).

Data Collection

Outcomes: The two outcomes of interest in the 3 months following LRTI diagnosis were respiratory infection-related admission (*ie*, a hospital admission for pneumonia or another LRTI) and respiratory infection-related mortality (*ie*, a death from pneumonia or another LRTI, or a death with an diagnosis of pneumonia or another LRTI recorded in the previous 7 days). The same codes were used in the outcome assessment as for the initial case identification (Appendix 1 of the online supplemental material).

Exposures: The effect of a range of exposures was investigated, including demographic factors, comorbidities and treatment. Recorded or calculated body mass index (BMI) was categorized into four groups, using US standards for children < 16 years of age[31] and the following categories for patients ≥ 16 years of age: underweight (< 20.0 kg/m^2); normal weight (20.0 to 24.9 kg/m^2); overweight (25.0 to 29.9 kg/m^2); and obese (≥ 30 kg/m^2).

Asthma, allergic rhinitis, and components of the Charlson comorbidity index[32] (myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, hemiplegia, diabetes, moderate or severe renal disease, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, or AIDS) were identified on the basis of appropriate codes recorded during the year before the index date. The numbers of recorded PCP consultations and specialist referrals or hospitalizations in the year before the index date were calculated as an assessment of health-care utilization to take account of the increased potential for patients to receive a common diagnosis if they consult more often.

Information on current pneumococcal and influenza vaccination status and on inhaled corticosteroids (ICSs) prescribed in the previous year was also recorded. Information on primary care antibiotic prescribing for LRTIs was collected on the index date and for the 7 days prior to the index date. For each prior antibiotic prescription, a likely indication was assigned on the basis of clinical codes recorded on the same day. The seasonality of the studied outcomes was evaluated using the following categories: winter (December, January, and February); spring (March, April, and May); summer (June, July, and August); and autumn (September, October, and November).

Statistical Analysis

Statistical analysis was conducted using a statistical software package (STATA, version 9.2 for Windows; Stata Corporation; College Station, TX). Graphs were made using appropriate software (SPSS, version 15.0 for Windows; SPSS Inc; Chicago, IL). The incidence of LRTI diagnosis, the antibiotic prescribing rate, and the rates of respiratory infection-related hospital admission and death during the 3 months following LRTI diagnosis were calculated in the study population overall and in 10-year age bands for male and female patients (the total number of cases divided by the number of patient-years of up-to-standard data in the GPRD during the study period for patients meeting the other inclusion criteria for the source population). Descriptive statistics were also investigated by month for the study population as a whole.

The magnitude of association between each outcome and each exposure was described by the hazard ratio (HR), the risk of an end point at any given time. HRs were estimated using survival analysis (a Cox proportional hazards model taking into account the aggregation of patients within practices). The Cox proportional hazards assumption was tested using the generalization formulated by Grambsch and Therneau[33] (STATA, version 9.2 for Windows; Stata Corporation) and was assessed graphically. Cox-Snell residuals were used to assess the overall model fit.

First, the association between individual factors and each outcome was assessed by univariate analysis. For each potential risk factor and each outcome, an HR adjusted for age, age squared (to take account of the increasing importance of age with increasing age), sex, National Health Service (NHS) region, and practice deprivation score was calculated. To take account of the possibility of confounding by indication in an observational study such as this, potential differences between patients to whom antibiotics had been prescribed and not prescribed were adjusted for using an antibiotic prescribing propensity score estimated using logistic regression. Patients who died on the index day were excluded from the analysis of factors associated with the prescribing of antibiotics on the index day, because they may have died before they had the opportunity to be prescribed an antibiotic. The fit of the model was assessed using the Hosmer-Lemeshow test.

The next step for each outcome was to select those variables that resulted in the most parsimonious model but explained as much variability as possible. A backward stepwise procedure was used for the selection of variables in the model, which included all factors associated with the outcome in the univariate analyses for which complete information was available in addition to age, age squared, sex, NHS region, practice deprivation score, and antibiotic prescribing propensity score. To account for the possibility that hospital admission for any reason on the index date could prevent antibiotic prescribing in primary care, we conducted supplementary analyses in which patients hospitalized on the index date were assumed to have been prescribed antibiotics on the index date in the hospital or were excluded from the multivariate model. Absolute risk reductions and numbers needed to treat (NTTs) were calculated as suggested by Altman and Kragh Andersen.[34]

Results

Study Population

The source population was drawn from 346 primary care practices, 55.2% of which had participated in the GPRD for > 10 years. Practices were distributed throughout the United Kingdom with even representation from areas with different levels of deprivation. From a source population of 2.9 million patients contributing a total of 2,886,007 person-years of follow-up during 2004, we identified a total of 167,680 patients consulting about an LRTI for the first time during 2004, of whom 151,088 satisfied the inclusion and data quality criteria. The study population had a median age of 54 years (interquartile range, 37 years) and was 57.1% female.

First LRTI Diagnosis

The rate of first LRTI diagnosis during the study year was 52.6 per 1,000 person-years overall (male patients, 45.6 per 1,000 person-years; female patients, 59.4 per 1,000 person-years). Rates of LRTI diagnosis were higher in patients 1 to 9 years of age than in those 10 to 19 years of age, increasing steadily with age thereafter (Fig 1). Over one third (37.7%) of LRTI diagnoses occurred in winter (December, January, and February) [Appendix 2 of the online supplemental material].

Antibiotic Prescription

Antibiotics were prescribed to 130,160 of the 151,088 patients (86.1%) on the day they received their diagnosis of LRTI, including 1,602 of the 2,401

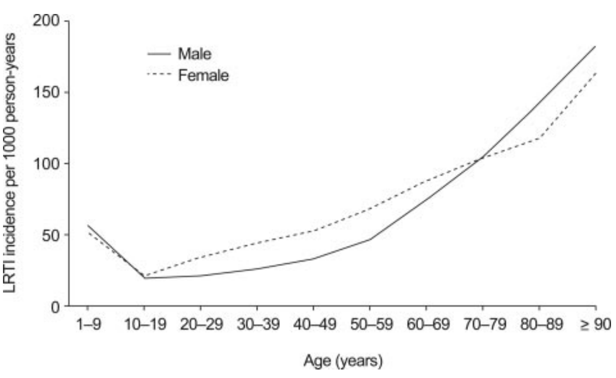

FIGURE 1. Rate of first consultation for LRTI in UK primary care settings in 2004 by age and sex.

patients (66.7%) admitted to the hospital on the index date and 19 of the 1,233 patients (1.5%) who died on the index date. Excluding the 1,233 patients who died on the index date, 128,539 of the 149,855 patients with LRTI (85.8%) were prescribed an antibiotic in the community. The most commonly prescribed antibiotics were penicillins (72.8%) and macrolides (15.5%). In a multivariate analysis adjusting for age, age squared, and sex, female patients and patients with asthma or an up-to-date influenza or pneumococcal vaccination had an increased likelihood of being prescribed antibiotics on the index date, while frequent health-care utilization and a number of chronic conditions were associated with a decreased likelihood of antibiotics being prescribed (Table 1). In total, 4,224 (2.8%) of the patients had received an antibiotic prescription in the previous 7 days before the LRTI diagnosis, and prior antibiotic prescribing was also associated with a markedly decreased likelihood of antibiotic prescribing on the index date. A likely indication was assigned to 2,400 of these prior antibiotic prescriptions, with the most common being cough (988 prescriptions; 26.5%) and upper respiratory tract infection (895 prescriptions; 24.0%) [Appendix 3 of the online supplemental material]. The indication for prior antibiotic prescribing was likely to have been LRTI (including influenza) in only 35 patients (0.9%) and was an unspecified respiratory tract infection in only 60 patients (1.6%).

Hospital Admission

In the 3 months following the first LRTI diagnosis, 20,311 patients (13.4%) were admitted to hospital, 1,147 of whom (5.6%) were admitted for respiratory infections. Most respiratory infection-related hospital admissions (614 hospital admissions; 53.5%) took place on the index date (Appendices 4 and 5 of the online supplemental material). Overall, the incidence of hospital admission related to pneumonia and other LRTIs was 0.40 per 1,000 person-years in the GPRD.

In univariate analyses, the following two factors were associated with a decreased risk of respiratory infection-related hospital admission: increasing BMI; and the prescription of any antibiotic on the day of diagnosis (Table 2). Four further factors were associated with an increased risk of respiratory infection-related hospital admission in univariate analyses, as follows: increasing age; antibiotic prescription in the 7 days before LRTI diagnosis; frequent consultation; and prior referral or hospitalization. In a multivariate model, the positive associations with prior antibiotic prescription and specialist referral or hospitalization and the negative association with antibiotic prescription on the index date remained significant (Table 2). The absolute risk reduction associated with antibiotic prescription on the index date was 0.10%, corresponding to an NTT to prevent one respiratory infection-related hospital admission of 1,002 (95% confidence interval [CI], 645 to 3,385). In age-stratified analyses, antibiotic prescription on the index date was associated with a significantly reduced risk of hospital admission among patients 18 to 64 years of age (HR, 0.61; 95% CI, 0.44 to 0.84) but not patients 1 to 17 years of age or ≥ 65 years of age (Appendices 6, 7, and 8 of the online supplemental material). The absolute risk reduction of 0.08% in this age group translated to a NNT of 1,222 (95% CI, 851 to 2,979).

Mortality

In the 3 months following LRTI diagnosis, 3,964 patients (2.6%) died, 2,126 of whom (53.6%) died of pneumonia or another LRTI. Most respiratory infection-related deaths (1,233; 60.0%) took place on the index date (Appendix 5 of the online supplemental material). The overall respiratory infection-related mortality rate was 0.74 per 1,000 person-years in the GPRD.

In univariate analyses, the following factors were associated with increased respiratory infection-related mortality: increasing age; smoking; increasing Charlson comorbidity index; prior antibiotic prescribing; frequent consultation and prior specialist referral or hospital admission (Table 3). The following factors were associated with a decreased respiratory infection-related mortality: female sex; cohabitation (marital status of cohabiting, engaged, married, remarried, or stable relationship vs divorced, separated, single, widowed, or living with a partner among those at least 16 years of age); overweight/obesity; alcohol consumption (any vs none among those at least 16 years of age); the presence of asthma or allergic rhinitis; current influenza vaccination; prior prescription of ICSs; and prescription of antibiotics on the index date.

In a multivariate model, the positive associations with increasing Charlson comorbidity index, prior antibiotic prescribing and consultation rate, and negative associations with female sex, allergic rhinitis, influenza vaccination, prior prescription of ICSs, and antibiotic prescription on the index date remained significant (Table 3). The absolute risk reduction associated with antibiotic prescription on the index date was 0.01%, corresponding to an NTT to prevent one respiratory infection-related death of 7,247 (95% CI, 6,757 to 7,937). In age-stratified analyses, antibiotic prescription on the index date was associated with a significantly reduced risk of

Table 1—*Factors Associated With an Antibiotic Prescription During a First Consultation for Lower Respiratory Tract Infection in Patients Who Survived the Index Date**

Factors	Antibiotic Prescribed (n = 128,539)		Antibiotic Not Prescribed (n = 21,316)		OR (95% CI)	
	No.	%	No.	%	Univariate Analysis†	Multivariate Analysis‡
Age						
1–19 yr	19,202	14.9	4,043	19.0	1	Continuous
20–39 yr	21,828	17.0	2,956	13.9	1.54 (1.45–1.65)	
40–59 yr	35,821	27.9	4,250	19.9	1.76 (1.64–1.89)	
60–79 yr	38,936	30.3	5,753	27.0	1.42 (1.30–1.55)	
≥ 80 yr	12,752	9.9	4,314	20.2	0.62 (0.55–0.69)	
Sex						
Male	54,861	42.7	9,429	44.2	1	1
Female	73,677	57.3	11,886	55.8	1.06 (1.02–1.09)	1.08 (1.04–1.11)
BMI§						
< 20 kg/m^2	8,102	6.3	1,536	7.2	0.91 (0.86–0.98)	
20.0–24.9 kg/m^2	32,240	25.1	5,089	23.9	1	
25.0–29.9 kg/m^2	32,094	25.0	4,780	22.4	1.07 (1.03–1.12)	
≥ 30 kg/m^2	21,416	16.7	3,052	14.3	1.09 (1.04–1.14)	
Smoking§	5,767	30.8	34,487	32.3	1.05 (1.01–1.10)	
Alcohol consumption§	77,109	80.3	11,424	77.5	1.08 (1.02–1.14)	
Comorbidity¶						
Asthma	17,459	13.6	2,593	12.2	1.08 (1.03–1.14)	1.10 (1.04–1.16)
Allergic rhinitis	5,393	4.2	793	3.7	1.09 (0.98–1.21)	
COPD	4,999	3.9	1,175	5.5	0.76 (0.71–0.83)	0.74 (0.68–0.80)
Any tumor	749	0.6	204	1.0	0.68 (0.58–0.80)	0.73 (0.62–0.86)
Metastatic solid tumor	59	0.0	22	0.1	0.45 (0.27–0.76)	0.55 (0.32–0.94)
Leukemia	20	0.0	9	0.0	0.42 (0.20–0.89)	
Lymphoma	31	0.0	22	0.1	0.23 (0.13–0.39)	0.25 (0.14–0.43)
Congestive heart failure	658	0.5	177	0.8	0.70 (0.60–0.82)	0.74 (0.64–0.86)
Dementia	217	0.2	67	0.3	0.67 (0.48–0.94)	
Hemiplegia	45	0.0	24	0.1	0.38 (0.22–0.65)	0.44 (0.26–0.75)
Vaccination¶						
Influenza	48,486	37.7	8,472	39.7	1.21 (1.16–1.27)	1.22 (1.17–1.29)
Pneumococcal	23,050	29.9	4,206	34.4	1.14 (1.07–1.21)	1.10 (1.03–1.18)
ICS prescription¶	27,427	21.3	4,376	20.5	1.04 (0.99–1.09)	
Antibiotic prescription in the previous 7 d	2,529	2.0	1,695	8.0	0.23 (0.22–0.25)	0.24 (0.22–0.25)
Consultations¶						
0–2	19,220	15.0	2,729	12.8	1	1
3–10	54,370	42.3	8,390	39.4	1.00 (0.95–1.06)	1.01 (0.96–1.06)
> 10	54,949	42.7	10,197	47.8	0.88 (0.83–0.94)	0.91 (0.85–0.98)
Referral/hospitalization¶	40,985	31.9	7,268	34.1	0.90 (0.86–0.94)	0.94 (0.89–0.98)
Season of index date						
Summer	21,584	16.8	3,608	16.9	1	
Autumn	28,413	22.1	4,666	21.9	1.03 (0.96–1.10)	
Winter	48,558	37.8	7,986	37.5	1.06 (1.01–1.12)	
Spring	29,984	23.3	5,056	23.7	1.03 (0.98–1.09)	

*OR = odds ratio. Of the 1,233 patients who were excluded from the analysis because they died on the index date, 19 were prescribed an antibiotic.

†Univariate ORs and 95% CIs were adjusted for age, age squared, and sex. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

‡Multivariate ORs and 95% CIs were adjusted by age, age squared, sex, and all other variables remaining in the model. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

§Analysis of smoking and alcohol consumption was conducted in patients at least 16 years of age. Data on BMI, smoking, and alcohol consumption were not available for 34,687 (27.0%), 5,361 (4.2%), and 18,872 (14.9%) patients, respectively, who were prescribed antibiotics on the index date, and for 6,859 (32.2%), 1,188 (5.6%), and 6,574 (15.8%) patients, respectively, who were not prescribed antibiotics on the index date.

¶Comorbidity (including COPD), influenza vaccination, ICS prescription, primary care consultations, and referral or hospitalization were analyzed in the previous year. Pneumococcal vaccination in the previous 10 years was analyzed in the subset of patients who had been registered with a practice for at least that period of time.

Table 2—*Association of Demographic and Lifestyle Factors, Comorbidity and Health-Care Utilization With Respiratory Infection-Related Hospital Admission Within 3 Months of First LRTI Diagnosis*

Factors	Admitted for Pneumonia or Other LRTI (n = 1,147)		Not Admitted for Pneumonia or Other LRTI (n = 149,941)		HR (95% CI)	
	No.	%	No.	%	Univariate Analysis*	Stepwise Multivariate Model†
Age group						
1–19 yr	184	16.0	23,062	15.4	1	Continuous
20–39 yr	103	9.0	24,691	16.5	0.70 (0.48–1.01)	
40–59 yr	254	22.1	39,862	26.6	1.08 (0.80–1.45)	
60–79 yr	379	33.0	44,641	29.8	1.46 (1.10–1.92)	
≥ 80 yr	227	19.8	17,685	11.8	2.28 (1.67–3.10)	
Sex						
Male	550	48.0	64,304	42.9	1	1
Female	597	52.0	85,635	57.1	0.86 (0.71–1.04)	0.83 (0.69–1.01)
Cohabitation status‡						
Living alone	68	25.9	8,598	30.3	1	
Living with partner	195	74.1	19,796	69.7	1.03 (0.72–1.45)	
BMI‡						
≤ 19.9 kg/m^2	76	10.0	7,990	7.8	1.20 (0.85–1.68)	
20.0–24.9 kg/m^2	305	40.1	36,460	35.5	1	
25.0–29.9 kg/m^2	243	32.0	35,906	35.0	0.65 (0.49–0.86)	
≥ 30.0 kg/m^2	136	17.9	22,344	21.8	0.72 (0.55–0.93)	
Smoking‡						
No	673	71.7	85,471	68.0	1	
Yes	265	28.3	40,212	32.0	0.85 (0.68–1.07)	
Alcohol consumption‡						
No	185	21.9	22,344	20.2	1	
Yes	660	78.1	88,484	79.8	1.08 (0.85–1.37)	
Charlson comorbidity index						
0	1,029	89.7	137,873	92.0	1	
1	89	7.8	9,601	6.4	1.08 (0.80–1.44)	
2–10	29	2.5	2,467	1.6	0.96 (0.52–1.78)	
Other comorbidity						
Asthma	153	13.3	19,986	13.3	1.14 (0.86–1.52)	
Allergic rhinitis	46	4.0	6,159	4.1	0.90 (0.57–1.42)	
Vaccination§						
Influenza	509	44.4	57,255	38.2	0.92 (0.74–1.14)	
Pneumococcal	276	40.1	27,398	30.6	1.03 (0.81–1.32)	
ICS prescription§	258	22.5	31,721	21.2	1.11 (0.89–1.38)	
Antibiotic prescription¶						
On the index date	633	55.2	127,901	85.3	0.69 (0.55–0.85)	0.73 (0.58–0.92)
In the past 7 d	122	10.6	4,167	2.8	2.21 (1.57–3.12)	1.92 (1.24–2.96)
Consultations§						
0–2	110	9.6	21,914	14.6	1	
3–10	413	36.0	62,701	41.8	1.06 (0.77–1.47)	
> 10	624	54.4	65,326	43.6	1.45 (1.06–1.97)	
Referral or hospitalization§						
No	657	57.3	101,595	67.8	1	1
Yes	490	42.7	48,346	32.2	1.48 (1.19–1.84)	1.48 (1.20–1.83)
Season of index date						
Summer	202	17.6	25,220	16.8	1	
Autumn	250	21.8	33,083	22.1	1.00 (0.76–1.33)	
Winter	422	36.8	56,555	37.7	0.89 (0.69–1.16)	
Spring	273	23.8	35,083	23.4	0.86 (0.66–1.22)	

*Univariate HRs and 95% CIs were adjusted for age (continuous), age squared, sex, NHS region, and practice deprivation score. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

†Multivariate HRs and 95% CIs were adjusted for age (continuous), age squared, sex, NHS region, practice deprivation score, antibiotic prescribing propensity score, and the following factors associated with hospital admissions for pneumonia in the univariate analysis: antibiotic prescription on the index date; antibiotic prescription in the 7 days prior to the index date; and specialist referral or hospitalization. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

‡Analysis of cohabitation status, alcohol consumption, and smoking was conducted in patients at least 16 years of age. Data on BMI, alcohol consumption, and smoking were not available for all patients.

§Influenza vaccination, ICS prescription, primary care consultations, and referral or hospitalization were analyzed in the previous year. Pneumococcal vaccination in the previous 10 years was analyzed in the subset of patients who had been registered with a practice for at least that period.

¶Antibiotic prescribing on the index date was analyzed in the subset of patients surviving the index date.

Table 3—*Association of Demographic and Lifestyle Factors, Comorbidity and Health-Care Utilization With Respiratory Infection-Related Mortality Within 3 Months of First LRTI Diagnosis*

Factors	Died From Pneumonia or Other LRTI (n = 2,126) No.	%	Did Not Die From Pneumonia or Other LRTI (n = 148,962) No.	%	HR (95% CI) Univariate Analysis*	Stepwise Multivariate Model†
Age group						Continuous
1–19 yr	2	0.1	23,244	15.6	1	
20–39 yr	18	0.8	24,776	16.6	7.7 (1.0–61.9)	
40–59 yr	90	4.2	40,026	26.9	26.7 (3.8–186.8)	
60–79 yr	583	27.4	44,437	29.8	133 (19–947)	
≥ 80 yr	1,433	67.4	16,479	11.1	842 (119–5975)	
Sex						
Male	968	45.5	63,886	42.9	1	1.00
Female	1,158	54.5	85,074	57.1	0.70 (0.61–0.80)	0.73 (0.64–0.84)
Cohabitation status‡						
Living alone	182	45.6	8,484	30.0	1	
Living with partner	217	54.4	19,764	70.0	0.68 (0.49–0.96)	
BMI‡						
≤ 19.9 kg/m^2	222	16.6	7,844	7.7	1.20 (0.85–1.68)	
20.0–24.9 kg/m^2	552	41.2	36,215	35.5	1	
25.0–29.9 kg/m^2	397	29.6	35,752	35.0	0.65 (0.49–0.86)	
≥ 30.0 kg/m^2	170	12.7	22,310	21.8	0.72 (0.55–0.93)	
Smoking‡						
No	1,435	79.0	84,709	67.9	1	
Yes	381	21.0	40,096	32.1	1.38 (1.13–1.68)	
Alcohol consumption‡						
No	508	33.4	22,021	20.0	1	
Yes	1,012	66.6	88,132	80.0	0.64 (0.53–0.78)	
Charlson comorbidity index						
0	1,751	82.4	137,151	92.1	1	1.00
1	239	11.2	9,451	6.3	1.07 (0.88–1.31)	1.03 (0.83–1.28)
2–10	136	6.4	2,360	1.6	2.75 (2.13–3.55)	2.24 (1.72–2.91)
Other comorbidity						
Asthma	144	6.8	19,995	13.4	0.58 (0.44–0.77)	
Allergic rhinitis	31	1.5	6,174	4.1	0.46 (0.27–0.80)	0.48 (0.27–0.83)
Vaccination§						
Influenza	1,406	66.1	56,358	37.8	0.71 (0.61–0.81)	0.75 (0.65–0.87)
Pneumococcal	733	51.4	26,941	30.4	0.88 (0.74–1.04)	
ICS prescription§	317	14.9	31,662	21.3	0.67 (0.55–0.80)	0.63 (0.52–0.76)
Antibiotic prescription¶						
On index date	458	21.5	128,076	86.0	0.29 (0.25–0.34)	0.31 (0.26–0.37)
In the past 7 d	146	6.9	4,143	2.8	2.56 (2.02–3.25)	1.56 (1.20–2.03)
Consultations§						
0–2	112	5.3	21,912	14.7	1	1.00
3–10	594	27.9	62,520	42.0	1.09 (0.75–1.57)	1.19 (0.82–1.74)
> 10	1,420	66.8	64,530	43.3	1.54 (1.06–2.24)	1.62 (1.09–2.40)
Referral or hospitalization§						
No	1,143	53.8	101,109	67.9	1	
Yes	983	46.2	47,853	32.1	1.29 (1.12–1.49)	
Season of index date						
Summer	387	18.2	25,035	16.8	1	
Autumn	426	20.0	32,907	22.1	0.97 (0.78–1.21)	
Winter	762	35.8	56,215	37.7	0.84 (0.69–1.02)	
Spring	551	25.9	34,805	23.4	0.97 (0.78–1.20)	

*Univariate HRs and 95% CIs were adjusted for age (continuous), age squared, sex, NHS region, and practice deprivation score. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

†Multivariate HRs and 95% CIs were adjusted for age (continuous), age squared, sex, NHS region, practice deprivation score, antibiotic prescribing propensity score, and the following factors associated with pneumonia admissions in the univariate analysis: antibiotic prescription on the index date; antibiotic prescription in the 7 days prior to the index date; and specialist referral or hospitalization. Unless otherwise stated, the reference category was the absence of the studied factor in each case.

‡Analysis of cohabitation status, alcohol consumption, and smoking was conducted in patients at least 16 years of age. Data on BMI, alcohol consumption, and smoking were not available for all patients.

§Influenza vaccination, ICS prescription, primary care consultation rate, and referral or hospitalization were analyzed in the previous year. Pneumococcal vaccination in the previous 10 years was analyzed in the subset of patients who had been registered with a practice for at least that period.

¶Antibiotic prescribing on the index date was analyzed in the subset of patients surviving the index date.

death among patients 18 to 64 years of age (HR, 0.21; 95% CI, 0.13 to 0.35) and at least 65 years of age (HR, 0.31; 95% CI, 0.26 to 0.37) [Appendices 9, 10, and 11 of the online supplemental material]. The corresponding absolute risk reductions were 0.02% and 0.01%, respectively, and the NNTs were 6,329 (95% CI, 5,747 to 7,693) and 14,493 (95% CI, 13,514 to 15,873), respectively.

Relationships Among Antibiotic Prescribing, Hospital Admissions, and All-Cause Mortality

Hospital admission or death for any reason on the index date could make antibiotic prescribing in primary care less likely. Because patients who are lost to follow-up on the index date do not contribute to Cox proportional hazards models, deaths on the index date are already taken into account in analyses of hospital admissions and mortality, and hospital admissions on the index date are taken into account in analyses of hospital admissions. Therefore, we conducted supplementary analyses addressing the relationship between hospital admissions on the index date and mortality. The prescription of antibiotics remained associated with reduced all-cause mortality when patients who were hospitalized on the index date were assumed to have been prescribed antibiotics on the index date in the hospital (HR, 0.38; 95% CI, 0.35 to 0.42) or were excluded from the multivariate model (HR, 0.37; 95% CI, 0.33 to 0.40).

Discussion

LRTI was a common cause of consultation in UK primary care settings in 2004, with approximately 5% of the population consulting a PCP about LRTI at least once during the year, which is a rate that is comparable to those reported by previous studies[6,35] conducted in the United Kingdom. The vast majority of patients (85.8%) were prescribed an antibiotic during their first consultation, as has been seen previously.[5] In contrast to the much-cited iceberg of community-acquired respiratory tract infection,[36] our study showed that more patients with LRTI die of pneumonia and other LRTIs (1.41%) than are admitted to the hospital with these diagnoses (0.76%), which is comparable with other findings.[37] The difference between mortality and hospital admissions was greatest in patients > 80 years of age, perhaps because many of them lived in elderly residential facilities and so were cared for outside a formal hospital setting. Nevertheless, the large proportion of respiratory infection-related hospital admissions and deaths occurring on the index date (53.5% and 57.9%, respectively) is a potential cause for concern because it suggests that patients with an LRTI may be consulting a PCP too late for such adverse outcomes to be avoided. Indeed, studies[38] have shown that more than four in five adults consult late in the course of an acute LRTI.

In line with previous studies,[39,40] increasing age was a risk factor for respiratory infection-related hospital admissions and death, while female sex reduced the risk of death (but not of hospital admissions). We interpret the nonsignificant increase in the risk of adverse outcome in patients with low BMI to mean that persons who were particularly thin or emaciated, probably as a result of chronic disease, are more likely to be hospitalized or die as a result of an LRTI. However, information on BMI (and also alcohol consumption and smoking status) was not available for all patients in the GPRD, and it may be recorded preferentially for patients who are least likely to become seriously ill. The effectiveness of influenza vaccination is the subject of much debate,[41] but influenza vaccination was associated with a clear reduction in respiratory infection-related mortality in our study. There was no evidence of the potential adverse effect of ICSs on the outcomes of LRTI.[42]

The only factor to be associated with a reduced risk of both hospital admissions and death related to respiratory infection in this observational study was antibiotic prescription on the day of diagnosis. One potential explanation for this observation is that PCPs may be less likely to prescribe antibiotics to patients who are at the greatest risk of adverse outcomes. Patients who were admitted to the hospital or died on the index date were indeed less likely to be prescribed an antibiotic than those managed in the community, most likely because PCPs did not prescribe antibiotics to patients they were about to admit to hospital. While outcomes on the index date were excluded from the statistical analyses, patients who did not receive antibiotics because they were about to be admitted to the hospital but whose hospital admission was delayed to a different day might have contributed to the most seriously ill patients not being prescribed antibiotics. It is possible that an elective decision not to undertake active treatment with antibiotics could have been made in patients who were the most at risk of adverse outcomes (*eg*, in those living in nursing homes with major comorbidity, poor prognosis, and poor quality of life). However, the association between the nonuse of antibiotics and adverse outcome was stronger in patients 18 to 64 years of age than in those ≥ 65 years of age.

The other potential explanation for our observation is that the prescription of an antibiotic for patients with LRTI may reduce the risk of subsequent adverse outcomes such as hospital admissions and mortality. While controversial, this explanation is plausible, given the difficulties in diagnosing pneumonia in primary care and the proven benefits of antibiotic therapy in patients with pneumonia. It is also supported by another observational study[18] involving data from the GPRD, which showed that antibiotic prescribing for LRTIs is associated with a reduced risk of pneumonia diagnosis. While the high NNTs we observed indicate that, for most patients, antibiotics are unnecessary, the clinical markers for potential hospital admission or death are not clear. A cautious approach may be needed, therefore, when considering which patients with an LRTI who consult a physician need to be prescribed an antibiotic, particularly in high-risk and vulnerable groups.

Our study was a large observational study reflecting everyday clinical management in a representative sample of UK primary care practices. We included two clinically meaningful end points, one (death) purely objective and the other (hospital admissions) affected by subjective factors, such as physician assessment of need and pressures on the health-care system. The cause of death recorded in the medical records held by the PCP is that entered on the death certificate, details of which are provided by the hospital for patients dying as inpatients. Cause-of-death information in the GPRD is audited,[43] and UK physicians are strongly discouraged from entering pneumonia as a cause of death unless there is objective evidence of this illness being the primary cause of death; other primary diagnoses are used in patients whose terminal event may be a respiratory infection but whose terminal illness was driven by other factors. Anecdotal evidence suggests that the recorded cause of hospital admission is perhaps less likely to be accurate, as hospital studies using hospital discharge diagnoses routinely identify a significant proportion of patients with an incorrect diagnosis. A particular strength of our analysis was the inclusion of all patients, regardless of age. Our data confirm that antibiotics are widely prescribed to children with LRTI in the community, and, although the vast majority of children with LRTI will have a viral illness, that bacterial pneumonia and other severe bacterial respiratory infections do occur in children, with no clear evidence base to guide practitioners in identifying those who are most at risk.

Our study is based on data routinely recorded by PCPs, and there is evidence that doctors choose diagnostic codes to justify their prescribing choices.[44] It would, therefore, be instructive to conduct a prospective epidemiologic survey, which could also take account of health-related quality of life and work productivity. Ultimately, however, a large, randomized, placebo-controlled trial of antibiotic therapy in representative patients with LRTI in the community is needed to help identify predictors of adverse outcomes of LRTI. Only with such information will the PCP be equipped to target antibiotics appropriately.

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