



Community-acquired pneumonia mortality: a potential link to antibiotic prescribing trends in general practice

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Summary Background: Community prescribing of antibiotics has decreased substantially in the UK in recent years. We examine the association between pneumonia mortality and recent changes in community-based antibiotic prescribing for lower respiratory tract infections (LRTI).

Methods: Retrospective analysis of aggregated data for pneumonia mortality, influenza incidence, and antibiotic prescribing for LRTI in England and Wales during 12-week winter periods between 1993/94 and 1999/2000.

Results: Winter antibiotic prescribing for LRTI showed a 30.0% decline since 1995/96. Over the same period, there was a 50.6% increase in winter excess pneumonia mortality adjusted for influenza incidence. Negative binomial regression analysis showed that the incidence of influenza alone had a significant association with winter pneumonia mortality ($P < 0.001$). The analysis also showed the reduction in antibiotic prescribing had a small but significant association with mortality ($P < 0.001$), when simultaneously modelling for influenza incidence.

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Conclusions: Our findings suggest an association between recent reductions in antibiotic prescribing for LRTI in general practice and an increase in pneumonia mortality in England and Wales. This retrospective study of aggregate data represents the first attempt to assess the effect of limiting antibiotic prescribing on patient outcomes, and highlights the need to identify which patients benefit from antibiotic treatment for LRTI.

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Introduction

Pneumonia is a major cause of morbidity and mortality worldwide. In the UK as a whole, pneumonia is responsible for over 10% of all deaths (66,581 deaths in 1999), the majority of which occur in the elderly.¹ In England, it accounted for 79,124 hospital admissions in 1999/2000, resulting in almost a million patient-days in hospital.¹ In the USA, 267 people per 100,000 population were hospitalised with community-acquired pneumonia (CAP) in 1991, with an overall case fatality rate of 8.8%.² In 1999, pneumonia and influenza were the seventh largest cause of mortality in the USA, accounting for a total of 63,730 deaths.³

Pneumonia morbidity and mortality show considerable seasonal variation. Pneumonia mortality rates are higher in the winter than the summer, and hospital admissions for pneumonia occur mainly during the winter months,^{4,5} putting a considerable burden on healthcare services through this period.⁶ The increased pneumonia morbidity and mortality seen during winter months can be expressed as a 'winter excess': the increase above the baseline levels of non-winter months. This excess is strongly influenced by the seasonal variations in influenza infection,^{4,5,7} because viral respiratory tract infection predisposes individuals to opportunistic bacterial infection.⁸ This link with bacterial infection suggests that winter excess pneumonia morbidity and mortality may be susceptible to changes in antibiotic prescribing practices.

In recent years, there have been worldwide efforts to reduce inappropriate antibiotic prescribing in response to mounting concerns about the emergence of antimicrobial resistance. In the UK, antibiotic prescribing has substantially decreased, particularly among the broad-spectrum penicillins and macrolides commonly prescribed for LRTI.^{9,10} Reductions in antibiotic prescriptions have also taken place in European countries,¹¹ while in the USA, large reductions have occurred among children,^{12,13} although data are not yet available for the US population as a whole.

To the best of our knowledge, no formal review of the impact of this reduction in antibiotic

prescriptions on morbidity and mortality has been planned or conducted to date. We therefore set out to investigate whether there was any association between recent changes in antibiotic prescribing for LRTI and winter pneumonia mortality in England and Wales.

Methods

Data sources

Pneumonia mortality

Pneumonia mortality data were obtained from the Office of National Statistics, using the 9th revision of the International Classification of Diseases (ICD-9) codes 480–486. These data exclude deaths from pneumonia as a consequence of underlying disease.¹⁴ Data prior to 1993/94 were omitted because of a change in ICD-9 mortality coding at the start of 1993.¹⁴ Similarly, data collection was not extended beyond 2000 because of a coding change to ICD-10 in January 2001 that may have confounded the analyses.¹⁵ All analyses were therefore performed using data for England and Wales from winter 1993/94 to winter 1999/2000.

We present winter pneumonia mortality data as a 'winter excess' value to exclude events that occur consistently throughout the year.¹⁶ A constant number of deaths was subtracted from winter values across all years to remove those not related to influenza, producing the winter excess value. The arbitrary constant used was 85% of the lowest summer pneumonia mortality value—equal to 7600 deaths for the 12-week study period. Using a constant enabled better quantification of events secondary to winter infectious agents without the introduction of additional bias. Annual totals for pneumonia mortality were also obtained for comparative purposes.

Influenza incidence

The incidence of influenza in the community was estimated from data on 'influenza and influenza-like illness' visits to the Royal College of General

Practitioners sentinel group of 70 general practices, and extrapolated to the population of England and Wales. The sentinel group is representative of general practices across England and Wales,¹⁷ and the clinical diagnoses it records have been shown to correlate strongly with laboratory-confirmed influenza infections.¹⁸ Patient demographic data within the group are comparable with census data, and with general practices as a whole.¹⁹ Collection of 12-week influenza data started 2 weeks prior to the 12-week collection period for mortality and antibiotic prescribing data. This allows time for secondary infection and progression to death to occur, and is standard practice when evaluating influenza-related outcomes.²⁰

Antibiotic prescribing

We obtained winter antibiotic prescribing data from the IMS Health UK MediPlus[®] database, which has also been used in recent antibiotic resistance studies.^{21,22} This database records deidentified weekly prescribing and patient morbidity data from a sentinel group of 462 general practices, which are monitored to ensure that they are representative of general practice as a whole.²³ Data regarding antibiotic prescriptions for LRTI [READ codes J13.0 (Pneumonia due to *Streptococcus pneumoniae*), J15.7 (Pneumonia due to *Mycoplasma pneumoniae*), J15.9 (Bacterial pneumonia, unspecified), J18.0 (Bronchopneumonia, unspecified), J18.2 (Hypostatic pneumonia, unspecified), J18.9 (Pneumonia, unspecified), J20.9 (Acute bronchitis, unspecified), J21.9 (Acute bronchiolitis, unspecified), J22.0 (Unspecified acute lower respiratory infection), J44.1 (Chronic obstructive pulmonary disease with acute exacerbations, unspecified), J44.8 (Other specified chronic obstructive pulmonary disease), J44.9 (Chronic obstructive pulmonary disease, unspecified), J40.0 (Bronchitis, not specified as acute or chronic), J41.0 (Simple chronic bronchitis), J41.1 (Mucopurulent chronic bronchitis), J42.0 (Unspecified chronic bronchitis) and J42.9 (Emphysema, unspecified)] were then extrapolated to the population of England and Wales. Annual totals for antibiotic prescribing for LRTI were also obtained for comparative purposes. These estimates were validated using Prescribing Analysis and Cost (PACT) data from the UK National Health Service (NHS) Prescription Pricing Authority (PPA). PPA data are provided by antibiotic type, not by indication or diagnosis, and are available only quarterly and for England alone. We therefore collected data for one quarter (January to March) for each winter and assumed that a constant

proportion (20%) of broad-spectrum penicillin and macrolide prescribing was for LRTI.

Population data

Annual population data for England and Wales were obtained from the Office of National Statistics.

Winter analysis period

The time period used for the analyses was derived from the findings of a Lung and Asthma Institute report commissioned by the UK Department of Health, which examined the seasonality of pneumonia mortality from 1991 to 1995.²⁴ The period selected was based on the criterion that mortality values be above the midpoint between the summer trough and the winter peak in pneumonia mortality. As a result, we chose a 12-week period starting at the beginning of December (week 48).

Statistical analyses

Negative binomial regression analysis was used to examine the change in winter mortality over time. This is a Poisson regression analysis with additional correction applied for any extra-Poisson dispersion. It was selected because it best reflected the shape of the assumed underlying distribution of pneumonia mortality. A Poisson distribution is a common assumption with count data leading to rate variables such as pneumonia mortality. The additional correction was applied to take into account a potential lack of independence of deaths caused by epidemic-like conditions often associated with influenza outbreaks.

We used a sequential model to assess the incremental contribution of influenza and antibiotic prescriptions to pneumonia mortality. As the incidence of influenza is known to be closely correlated with winter pneumonia mortality, it was included as the primary predictor. The rate of antibiotic prescribing for LRTI was included as the secondary predictor. The resultant coefficients were calculated as log rate ratios and converted to rate ratios.

Sensitivity analyses were performed in order to investigate the robustness of the results in the face of alternative data sources or data extraction methods. The first sensitivity analysis included an additional temporal variable in the regression analysis to detect any unspecified factors that might be changing progressively across the years. Two further analyses were conducted in which the time period analysed was extended equilaterally to 16 and 20 weeks.

In addition, two alternative regression models were used to gauge the robustness of the data analysis. Analyses were performed using a Poisson regression model with robust standard errors (a less conservative approach than the negative binomial regression) and a least-squares regression (a more conservative approach as it assumes a normal distribution, which is not likely in the case of death rates).

All data included in the regression analysis were expressed as rates per 1000 of the population of England and Wales for each year. Statistical analyses were performed using Stata version 6 software.

Results

Trends in winter pneumonia mortality

Data from the Office of National Statistics showed an almost two-fold variation in pneumonia mortality during the 12-week winter period across the 7 years of investigation (Fig. 1). The incidence of influenza for the corresponding period showed a high degree of correlation with pneumonia mortality ($r = 0.91$), with the mortality curve closely resembling that of community influenza (Fig. 1). In contrast, when pneumonia mortality and influenza data were examined over a 12-week summer period, pneumonia deaths appeared quite independent of influenza levels (Fig. 1).

Winter pneumonia mortality for each year was standardised to average influenza levels purely to allow year-by-year trends to be visualised. This revealed that winter excess pneumonia mortality for the 12-week periods increased by 50.6%

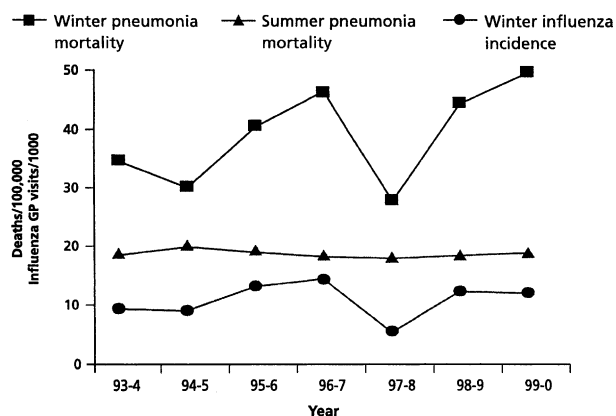


Figure 1 Variations in influenza incidence and pneumonia mortality during the 12-week winter analysis period between 1993/94 and 1999/2000.

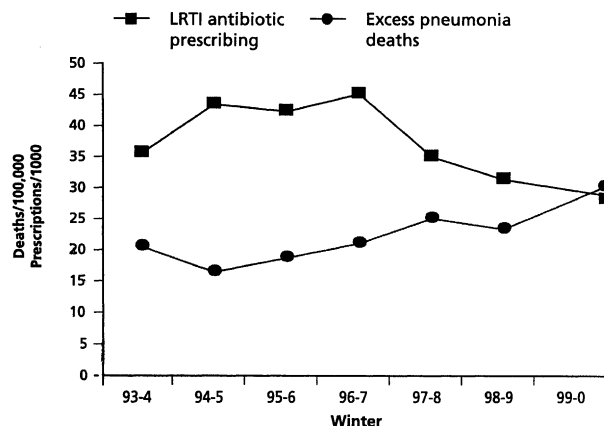


Figure 2 Trends in antibiotic prescribing for lower respiratory tract infection and excess winter pneumonia mortality. To take into account the large effect of influenza on winter pneumonia mortality, the data were standardised to the average influenza incidence over the analysis period (1993/94–1999/2000) using the actual data for each year (i.e. divide by the actual influenza incidence then multiply by the average influenza incidence of 9.95 visits/1000 population).

between 1995/96 (shortly before the fall in antibiotic prescribing) and 1999/2000, from 20.4 deaths/100,000 to 30.7 deaths/100,000 (Fig. 2). IMS data for the same winter periods showed a 30.0% decline in community antibiotic prescriptions for LRTI, from 42.3 prescriptions/1000 in 1995/96 to 29.6 prescriptions/1000 in 1999/2000 (Fig. 2).

The IMS antibiotic prescribing data were validated with 13-week antibiotic data (January to March) obtained from the PPA. The two data sets showed identical trends in winter community antibiotic prescriptions from winter 1993/94 to 1999/2000. A strong correlation was observed between the two data sets ($R^2 = 0.85$).

Regression analysis of winter pneumonia mortality data

Negative binomial regression analysis of the raw 12-week winter data showed that the incidence of community influenza alone was significantly associated with excess winter pneumonia mortality ($P < 0.001$; Table 1). When the model included both influenza and antibiotic prescribing as variables, the reduction in antibiotic prescribing for LRTI was significantly associated with mortality ($P < 0.001$; Table 1).

The results of the negative binomial regression analysis indicated that antibiotic prescribing for LRTI had a smaller effect on winter pneumonia mortality than influenza incidence. Nevertheless,

Table 1 Incremental results of negative binomial regression models (Stata v6).

Effect	Estimated rate ratio*	95% CI	P value	R ² †
Influenza visits/1000‡	1.123	1.077, 1.171	<0.001	0.082
Influenza visits/1000‡	1.136	1.119, 1.153	<0.001	0.187
Antibiotic prescriptions/1000¶	0.974	0.966, 0.981	<0.001	

*Calculated from the estimated log-rate ratios.

†Pseudo-R² reported for negative binomial regression models.

‡Visits to the general practitioner for influenza or influenza-like illness.

¶The antibiotic effect in the complete model, 0.974, is the ratio of the rate of change of mortality to the rate of change of antibiotic prescribing, i.e. deaths/1000 population for 1 script/1000 change in prescribing. Therefore a ratio of 1.00 would indicate no effect. The ratio appearing in one row is adjusted for the variables present in the other rows of the model, in this case for the effects of background influenza rate and year effect. The ratio shown here is below 1.00, indicating an increase in the mortality for a decrease in the prescribing rate. Note that changes in the rate of prescribing affect the rate of mortality in a multiplicative, i.e. non-linear, way.

Table 2 Sensitivity analyses using negative binomial regression models.

Alternative analysis	Effect	Estimated rate ratio*	95% CI	P value	R ² †
Extending winter period to 16 weeks (starting in week 46)	Influenza visits/1000‡	1.096	1.064, 1.130	<0.001	0.096
	Antibiotic prescriptions/1000	0.978	0.968, 0.989	<0.001	
Extending winter period to 20 weeks (starting in week 44)	Influenza visits/1000‡	1.078	1.044, 1.113	<0.001	0.079
	Antibiotic prescriptions/1000	0.978	0.966, 0.988	<0.001	
Inclusion of temporal variable	Influenza visits/1000‡	1.131	1.115, 1.148	<0.001	0.200
	Antibiotic prescriptions/1000	0.978	0.969, 0.987	<0.001	
	Temporal effect	1.019	0.993, 1.046	0.155	

*Calculated from the estimated log-rate ratios.

†Pseudo-R² reported for negative binomial regression models.

‡Visits to the general practitioner for influenza or influenza-like illness.

when a typical reduction in winter antibiotic prescriptions for LRTI of 10 prescriptions/1000 (Fig. 2) is applied to a constant influenza consultation rate of 9.95 visits/1000 (the mean for the study period), the model predicts an increase in winter pneumonia mortality of 3195 across the winter period (assuming a population of 50 million for England and Wales), independent of changes in other determinants. This equates to approximately one extra death from CAP for every 160 fewer winter antibiotic prescriptions for LRTI in general practice.

Sensitivity analyses confirmed that our conclusions are robust. The temporal variable, included to detect any unspecified factors changing progressively from year to year (for example, the effects of an ageing population), had no significant effect on pneumonia mortality ($P = 0.155$). Furthermore, the inclusion of this variable in the model did not alter

the effect of influenza or antibiotic prescribing upon pneumonia mortality (both remained $P < 0.001$), although the magnitude of the antibiotic effect (2609 additional deaths) is reduced slightly. Similarly, extending the data period equilaterally from 12 weeks to 16 weeks and 20 weeks had little effect on the results (Table 2).

Data analyses using alternative regression models also support the robustness of our findings. Both the influenza effect and the antibiotic prescribing effect were significant when the data were analysed by Poisson regression with robust standard errors (influenza effect, $P < 0.001$; antibiotic prescribing effect, $P < 0.001$) and by normal distribution least-squares regression (influenza effect, $P = 0.002$; antibiotic prescribing effect, $P = 0.026$; Table 3). The comparatively small R² values observed with the negative binomial regression compared with these two models reflect the large

Table 3 Results using alternative regression models.

Alternative regression models	Effect	Estimated effects*	95% CI	P value	R ² †
Poisson regression with robust standard errors	Influenza visits/1000‡	1.139	1.120, 1.158	<0.001	0.959
	Antibiotic prescriptions/1000	0.974	0.964, 0.984	<0.001	
Least-squares linear regression	Influenza visits/1000‡	0.0267	0.0167, 0.0367	0.002	0.903
	Antibiotic prescriptions/1000	-0.0062	-0.0112, -0.0012	0.026	

*Rate ratio in the case of Poisson regression, slope coefficient in the case of linear regression.

†Pseudo-R² reported for negative binomial regression models.

‡Visits to the general practitioner for influenza or influenza-like illness.

variance applied in the conservative negative binomial regression method.

Discussion

The key finding to emerge from our study is the significant association between the extent of antibiotic prescribing for LRTI and winter pneumonia mortality. Our results suggest that, when simultaneously modelled with influenza incidence, the increase in excess winter pneumonia mortality seen in recent years is associated with a reduction in antibiotic prescriptions for LRTI. However, care must be taken when interpreting the results of this study, given that it involved aggregate data from across England and Wales, and therefore cannot be used to determine cause and effect, and that the findings are based on the limited number of data points available between recent changes in mortality coding.

Initial investigations showed that, if the mortality data were standardised to the average influenza incidence, there was a 50.6% increase in excess winter pneumonia mortality between 1995/96 and 1999/2000. Our analysis showed that winter antibiotic prescribing for LRTI declined by 30.0% over the same period, a finding that appears to be confirmed by data from the PPA.

Regression analysis revealed that the incidence of community influenza had a significant effect on the variations in excess winter pneumonia mortality in England and Wales from 1993 to 2000. The exact magnitude of summer pneumonia mortality used in calculating this winter excess does not affect this statistical relationship, only the percentage change in mortality over time. The association between pneumonia and influenza is already well

established, both statistically and aetiologically.^{5,8,25} It is this link with pneumonia, rather than the relatively small disease burden of influenza itself, that provides the rationale for influenza vaccination of the elderly, the immunocompromised and those with underlying lung and cardiovascular disease.²⁶

The regression analysis also showed that the extent of antibiotic prescribing for LRTI had a small but significant association with pneumonia mortality. The concurrent significant effects of influenza and antibiotic prescribing occurred over and above any linear changes over the same period (for example, those progressive changes that might result from an ageing population, the spread of resistance, or changing patterns of healthcare), which were accounted for by a separate temporal variable. Furthermore, the results were robust in the face of different methods of data extraction and analysis. Nevertheless, it is not possible to exclude some possible confounding factors, such as changing patterns of diagnosis over the period studied.

Annual data from the PPA show that total antibiotic prescribing in England has fallen by just under one quarter, from a peak level of 44.5 million prescriptions in 1995/96 to 34.2 million prescriptions in 1999/2000.⁹ A recent study showed that this decline occurred across all age groups.¹⁰ Our study identified a reduction in winter antibiotic prescribing for LRTI of almost one-third. Similar trends were seen in a sample of general practices in the West Midlands region of England between 1993 and 1997, which showed a sharper decline in antibiotic prescribing for LRTI than in overall antibiotic prescribing.²⁷

The substantial decrease in antibiotic prescribing for LRTI appears surprising, given that the focus of recent advice from the UK government has been to

reduce antibiotic prescribing for upper respiratory and urinary tract infection rather than LRTI.²⁸ A systematic review of the small number of relevant randomised controlled trials concludes that antibiotics have a modest benefit in treating symptoms of LRTI,²⁹ suggesting that delays in antibiotic prescribing are unlikely to cause harm in most LRTI patients. However, for the small minority who develop pneumonia, delayed or insufficient antibiotic treatment is an important prognostic factor.^{30–32}

Although comprehensive guidelines on the diagnosis and treatment of pneumonia have recently been published in the UK,³³ it is difficult to diagnose pneumonia in general practice.³³ Given this, it is important to be able to identify which patients with LRTI are potentially at risk from pneumonia if not treated promptly. There is, therefore, an urgent need for retrospective case control studies and large prospective randomised clinical studies to identify those patients with LRTI who will selectively benefit from antibiotics and allow the development of appropriate treatment guidelines for LRTI.

A number of other questions raised by the present study also need to be addressed, in particular whether or not the association is causal. Further research is needed to determine whether the decline in prescribing and increase in mortality occur in particular groups of patients (e.g. the elderly) and to identify whether the effect is limited to certain groups of prescribers. Factors such as changing patterns of disease (e.g. antimicrobial resistance, influenza virulence, pneumococcal infection or respiratory syncytial virus infection), of healthcare (e.g. changing thresholds for admission to hospital), and of diagnosis and death certification (e.g. diagnosis of pneumonia versus acute exacerbation of chronic obstructive pulmonary disease) may have had an effect and need to be investigated. In particular, influenza and pneumococcal vaccination campaigns in the UK in recent years^{34,35} would be expected to reduce winter pneumonia mortality over the study period. In a survey of general practices in Scotland, influenza vaccination rates increased by more than 50% between 1993 and 1999 (from 72.2 doses per 1000 population to 111.0 dose/1000), while pneumococcal vaccination increased 26-fold (from 1.9 doses/1000 to 50.1 doses/1000) over the same period.³⁵

The findings of this study have implications for healthcare practice beyond England and Wales. The need to reduce inappropriate antibiotic prescribing to combat microbial resistance is recognised worldwide, and reductions in antibiotic prescribing have

been seen in other European countries¹¹ and among children in the US.^{12,13} Our findings suggest a need for studies examining the changing patterns of antibiotic prescribing and their effects on patient outcomes in other countries. Such studies may provide a useful comparison with the changes observed in England and Wales, and could help to improve antibiotic prescribing practices worldwide.

In conclusion, our findings suggest that there may be an association between changes in antibiotic prescribing for lower respiratory tract infection in general practice and changes in pneumonia mortality in England and Wales, although it is important to note that the association is not necessarily causal, and could be due to an as yet unidentified confounding factor. Further research into the effects of controlling antibiotic use on the outcomes of respiratory infections is therefore warranted, especially in patients at high risk of complications.

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