Antibiotic prescribing and admissions with major suppurative complications of respiratory tract infections: a data linkage study

Paul Little, Louise Watson, Stephen Morgan and Ian Williamson

SUMMARY

Background: *Systematic reviews of antibiotic treatment of common acute respiratory tract infections (RTIs) suggest modest symptomatic benefit, but provide limited evidence that prescribing prevents complications.*

Aim: *To assess the relationship between penicillin prescribing (the most commonly used group of antibiotics for RTIs) and hospital admission with complications.*

Design of study: Data linkage study.

Setting: *Ninety-six health authorities of England for the year 1997–1998.*

Method: *Hospital admissions related to RTIs were linked with prescribing analysis and cost (PACT) data.*

Results: *There was close correlation between items of penicillin use and total antibiotic use (r = 0.96). After controlling for SMR, age, sex, and Townsend score, a one-unit increase in penicillin use (items dispensed per capita) was associated with a reduction in annual incidence per 10 000 of admissions for quinsy (-3.55 admissions, 95% confidence interval [CI] = -6.85 to -0.26), and mastoiditis (square root of incidence of admissions = -1.05, 95% CI = -1.82 to -0.27). This does not represent lower referral thresholds among higher prescribers as higher prescribing was associated with more admissions for tonsillectomy and overall admissions. Increasing prescribing by 2000 items of penicillin for a practice of 10 000 patients could possibly prevent one admission for either mastoiditis or quinsy.*

Conclusion: *Higher antibiotic prescribing is associated with significantly fewer admissions with major complications. However, the overall size of the effect is modest and it is difficult to advocate an overall increase in prescribing to prevent complications. Future research should concentrate on finding better methods of targeting antibiotics to individuals at risk of poor outcome.*

Keywords: *antibiotics; prescribing; respiratory tract infections; hospital admission rate; complications.*

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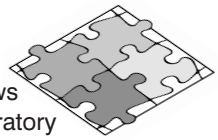
Introduction

ACUTE respiratory tract infections (RTIs) are the most common reason for patients to seek medical advice and for antibiotics to be prescribed.[1] Furthermore, attendance is increasing.[1] The current major concern is that with few new classes of antibiotics being developed, the inappropriate use of antibiotics for usually self-limiting conditions will foster the development of antibiotic resistance[2-4] and lead to serious infections becoming untreatable.[5,6] Thus it is currently an international priority not to encourage the use of antibiotics unless there is very good evidence of their efficacy.

There is growing evidence from systematic reviews of treatment trials of acute respiratory infections — acute tonsillitis/pharyngitis, otitis media, bronchitis, sinusitis — that the benefits of antibiotic for symptom resolution are likely to be modest for most patients.[7-14] However, owing to the rarity of major complications there is very little evidence about preventing such complications; one of the problems in persuading doctors to reduce antibiotic use in an increasingly litigious environment is the concern about serious complications from acute infection.[15] The only systematic review of RTIs powerful enough to document complications[14] is difficult to apply in practice. This review relies for most of its data on one study of patients with tonsillitis (providing 76% of the weighting) who were systemically unwell enough to be admitted to hospital shortly after the Second World War, when the prevalence of quinsy in untreated patients was very high (1:18). Clearly, this data cannot be extrapolated to the majority of patients presenting from healthier modern populations who are not systemically unwell, are treated with oral antibiotics, and where the prevalence of quinsy is much lower (approximately 1:400). Furthermore, the estimates derived from efficacy trials may not apply in the 'routine' settings: patients in everyday practice are not as rigorously controlled or monitored as in trial settings, will comply less with antibiotic treatment, and hence antibiotics will be less likely to prevent complications. A small study of routine data in two practices suggests that most patients who develop quinsy do so despite penicillin.[16] Thus there is a pressing need to clarify whether prescribing in everyday practice prevents complications for all the common respiratory infections.

To date, we are not aware of any study using the available large 'routine' data sets to assess the relationship between prescribing and major suppurative complications of RTIs when controlling for demographic differences in populations. In England, there are approximately 100 health authorities where data are aggregated by the Department of Health

HOW THIS FITS IN



What do we know?

Evidence from systematic reviews of treatment trails of acute respiratory infections show that the benefits of antibiotic for symptom resolution are likely to be modest for most patients. However, persuading doctors to reduce antibiotic use has been difficult in an increasingly litigious environment where there is the concern about serious complications from acute infection. There is a need to clarify whether prescribing in everyday practice prevents complications for all the common respiratory infections.

What does this paper add?

The results suggest that higher antibiotic prescribing is associated with fewer admissions with complications in the routine setting. However, the overall size of the effect is modest and it is difficult to advocate an overall increase in prescribing to prevent complications. Thus there is an urgent need to find better methods of targeting antibiotics to individuals at risk of poor outcome without increasing overall antibiotic use.

(DoH) for complications (using the hospital episode statistics data) and by the Prescription Pricing Authority (PPA) for antibiotic prescribing in primary care (prescribing analysis and cost [PACT] data). A data linkage study provides an important opportunity to address a key hypothesis: if prescribing reduces complications in the routine setting then health authorities with higher prescribing doctors should have lower rates of complications when controlling for confounding variables.

Method

Health authority hospital admission data (covering the year 1997–1998) for acute RTIs, complications of RTIs, operations relating to RTIs, and demographic data (standardised morbity ratio [SMR], Townsend material deprivation index,[17] age, sex) were provided by the DoH. The conditions requested were based on the ICD10 classification for complications and the Office of Population Censuses and Surveys (OPCS) classification of operations used by the DoH (Box 1). We have listed these conditions as 'complications' of RTI, but in reality they may represent either complications or new presentations of a more serious infection. Meningitis was included as a respiratory infection because the infection commences in the respiratory tract. Similarly, septicaemia can come from other sites (for example, skin, gut, urinary tract) but also commonly originates in the respiratory tract. Other potential complications of respiratory tract infections — for example, lateral sinus thrombosis, cavernous sinus thrombosis, subdural and epidural abcess, brain abcess, periorbital infections — were not included since they are much rarer, and also not specific to respiratory infections.

The PACT data for all groups of antibiotics, which documents dispensing of antibiotics in primary care, were requested at the health authority level for the same year (1997–1998) from the PPA.

Sample size calculation

For 80% power and 95% confidence using the NQuery sample size program, to detect a modest but clinically important correlation or partial correlation of 0.3 between penicillin prescribing and complications, we estimated that we would need matched data from at least 82 health authorities.

Analysis

The incidence of admissions is presented using medians and interquartile ranges since, for some of the rarer complications, the data were skewed. We used multiple linear regression in SPSS for Windows (version 8) to assess the relationship between items of penicillin use and the different categories of hospital admission, when controlling for potential confounding owing to age, sex, deprivation, and morbidity (using SMR as a proxy measure of the health of the population). We used standard graphical techniques to assess the assumptions that residuals were approximately normally distributed, had no relationship with the independent variable, and had homogeneous variance. If appropriate, the data was transformed by taking square roots of the dependent variable (square root rather than log transformation was used since, for some complications, there were zero values for some health authorities).

Results

We were able to obtain paired data (complications and PACT) for 96 health authorities for 1997–1998. The median incidence (interquartile range) for the common admissions related to the most common respiratory infections is given by age in Table 1. Admissions with rheumatic fever were so rare (mean = 1.4 per million) that they cannot be presented in the same table. The most common complication of respiratory illness of major public health importance is pneumonia, and the most common reason for admission is acute uncomplicated RTIs. The other major uses of secondary care are operations for the chronic/recurrent complications of RTIs (admissions for tonsillectomy and drainage of the middle ear).

There was close correlation between items of penicillin use and total antibiotic use (r = 0.96). We chose items of penicillin dispensed as our principal independent variable, as penicillins are the most common drug group used for RTIs.[18-20] Macrolides and tetracyclines are generally second-line drugs for RTIs (and also used in skin infections and acne), and quinolones are mainly used in urinary tract infections. The mean number of items of antibiotics dispensed per capita was 0.84 (SD = 0.13; minimum 0.55, maximum 1.15) and for penicillin the mean was 0.48 (SD = 0.08; minimum = 0.33; maximum = 0.69) — 57% of all antibiotic use.

The unadjusted and adjusted β-coefficients (with their confidence intervals) relating prescribing of penicillins to admissions are shown in Table 2. This shows the importance of controlling for sociodemographic variables, since there is no relationship between prescribing and complications in univariate analysis. However, increased penicillin use (items per capita) is associated with a significant reduction in admissions for both quinsy and mastoiditis when demographic variables are controlled for (see adjusted estimates in Table 2). This is unlikely to be owing to the referral threshold being greater among higher prescribers, since

Table 1. Median annual incidence (interquartile range) per 10 000 residents of the health authority of hospital admission with acute uncomplicated RTIs, common complications of RTIs, and operations relating to RTIs.

	Age range (years)				All ages
	0–14	15–44	45–64	65+	
Complications					
Quinsy	0.64 (0.39–0.99)	2.47 (2.09–2.98)	1.11 (0.75–1.47)	1.14 (0.69–1.70)	1.66 (1.34–1.90)
Mastoiditis	0.28 (0.16–0.53)	0.09 (0.05–0.16)	0.12 (0.00–0.19)	0.03 (0.0–0.20)	0.14 (0.09–0.20)
Pneumonia	12.6 (10.4–14.5)	4.59 (3.90–5.39)	10.6 (8.9–13.1)	71.3 (60.4–88.5)	18.2 (15.6–21.0)
Septicaemia	0.86 (0.64–1.17)	0.48 (0.31–0.66)	1.72 (1.18–2.36)	9.7 (7.2–12.4)	2.37 (1.85–2.77)
Acute respiratory infections (RTIs)					
Acute tonsillitis, sinusitis bronchitis, otitis media	127 (92 –147)	14.8 (11.5–17.5)	17.2 (13.3–21.5)	65.2 (56.4–81.9)	44.2 (35.9–56.2)
Meningitis	3.2 (2.49–4.07)	0.50 (0.33–0.68)	0.29 (0.13–0.41)	0.25 (0.14–0.51)	0.97 (0.74–1.20)
Operations related to RTIs					
Repair of ear drum	1.96 (1.30–2.79)	1.60 (1.22–2.28)	1.49 (0.97–2.12)	0.36 (0.20–0.65)	1.53 (1.14–2.00)
Mastoidectomy	0.83 (0.59–1.21)	0.88 (0.58–1.21)	1.00 (0.67–1.37)	0.58 (0.31–0.74)	0.86 (0.62–1.15)
Drainage of middle ear (including grommets)	53.2 (43.9–63.5)	1.74 (1.37–2.25)	2.11 (1.57–2.87)	1.62 (1.04,2.24)	11.9 (9.7–13.5)
Maxillary sinus drainage	0.0 (0.0–0.07)	0.11 (0.06–0.21)	0.19 (0.06–0.38)	0.09 (0.00–0.22)	0.11 (0.07–0.21)
Tonsillectomy	38.8 (31.6–48.5)	13.7 (11.2–16.3)	1.00 (0.78–1.26)	0.38 (0.16–0.58)	12.5 (10.6–15.0)

Table 2. Linear regression models. Estimated change (β-coefficient; 95% confidence intervals for β) in annual incidence of hospital admission (per 10 000 health authority residents) related to penicillin use in primary care.[a]

	Crude (95% CI)	Adjusted (95% CI)[b]	*t* (*P*-value)
Complications			
Quinsy	0.34 (-1.21 to 1.88)	-3.55 (-6.85 to -0.26)	2.14 (0.035)
Rheumatic fever[c]	0.02 (-0.22 to 0.26)	-0.23 (-0.75 to 0.29)	0.86 (0.39)
Mastoiditis[c]	0.09 (-0.28 to 0.46)	-1.05 (-1.82 to -0.27)	2.69 (0.009)
Pneumonia	6.9 (-4.2 to 17.9)	-11.0 (-34.3 to 12.2)	0.95 (0.35)
Septicaemia	0.39 (-1.44 to 2.23)	-2.03 (-6.03 to 1.97)	1.01 (0.32)
Anaphylaxis	0.01 (-0.10 to 0.13)	0.04 (-0.12 to 0.20)	0.49 (0.63)
Acute respiratory infections (RTIs)			
Acute tonsillitis, sinusitis bronchitis, otitis media	86.2 (56.2 to 116.1)	35.6 (-21.7 to 92.9)	1.24 (0.22)
Meningitis	1.22 (0.40 to 2.03)	-0.53 (-2.22 to 1.17)	0.62 (0.54)
Operations related to RTIs			
Repair of ear drum	3.44 (1.96 to 4.92)	0.83 (-2.35 to 4.02)	0.52 (0.60)
Mastoidectomy	1.16 (0.49 to 2.63)	-1.72 (-3.96 to 0.52)	1.53 (0.13)
Drainage of middle ear (0–14 age group)	3.95 (-38.1 to 46.0)	34.8 (-41.2 to 110.9)	0.91 (0.37)
Maxillary sinus drainage[c]	-0.55 (-1.36 to 0.27)	-0.73 (-2.47 to 1.00)	0.84 (0.40)
Tonsillectomy	20.9 (11.9 to 29.9)	21.1 (2.30 to 39.94)	2.23 (0.028)
All medical and surgical admissions	104.0 (59.8 to 148.1)	12.5 (-70.7 to 95.8)	0.30 (0.77)

[a]Penicillin use: items of penicillin dispensed per capita. [b]Adjusted for Townsend deprivation index (quintiles), percentage in each age group (4 bands from Table 1), SMR (quintiles), and percentage male. [c]Using the square root transformation of the dependent variable.

increased prescribing was associated with a significant increase in admissions for tonsillectomy, with a small non-significant increase in overall admissions.

Discussion

This study demonstrates that prescribing of penicillins in everyday practice is associated with fewer admissions for both quinsy and mastoiditis but higher rates of tonsillectomy and other referrals. Before the results are discussed the limitations of the study will be described.

Routine data

There are limitations in the accuracy of admissions data, particularly for complicated medical admissions. However, for acute infections — especially quinsy, mastoiditis — and for routine tonsillectomy the errors are less likely to be significant. Furthermore, internal audit of notes by the National Health Service Information Authority (NHSIA, Loughborough) showed that 80–90% of coded results are an accurate summary of the main reason for admission (personal communication, NHSIA. Similarly, PACT data solely relates to dispensing, not the use of, drugs — although dispensing is a reasonable marker of the intention to treat. We also have only a crude control for deprivation (Townsend index) and morbidity (SMR). However, measurement error (for coded admission, confounders, PACT) would reduce the observed effect and thus cannot explain the findings.

A single independent prescribing variable for all conditions?

A single PACT prescribing variable would only be related to all complications of all RTIs if doctors who prescribe for one RTI (for example, sore throat) also prescribe for other RTIs. We have preliminary survey evidence from 600 GPs suggesting that high prescribers for tonsillitis do also prescribe more for the other RTIs.

Respiratory infections	
J20, J22	Acute LRTI or acute bronchitis
H65, H66	Otitis media non-suppurative and suppurative
J03, J02	Acute tonsillitis, pharyngitis
J00, J06	Uncomplicated RTI unspecified and nasopharyngitis
J32 JO1	Sinusitis
G00, A39	Meningitis
Complications	
J36 and J39	Quinsy, peritonsillar abscess, peritonsillar cellulitis
I00 I01	Rheumatic fever (with and without heart involvement specified)
H70	Mastoiditis
A40, A41	Septicaemia
J13, J14, J15, J18	Pneumonia
Operations	
D14	Repair of ear drum
D10/D12.1	Mastoidectomy
D15.1	Drainage of middle ear
E12.2, E12.3, E13.1	Maxillary drainage
F34	Tonsillectomy

Box 1. ICD10 classification for complications and OPCS classification of operations used by DoH.

Does the admission rate really reflect complications?

In the case of pneumonia, many patients are managed in the community and thus admission rates may reflect differences in thresholds for admission. The same will apply to admissions for routine operations (middle ear drainage, tonsillectomy). However few patients with quinsy are managed in the community since they require surgery or intravenous antibiotics for peritonsillar cellulitis, and most children with mastoiditis are very unwell and will also be admitted for intravenous antibiotics. Thus the main findings of a reduction in quinsy and mastoiditis should not be affected significantly by differing thresholds of admission. Furthermore, the results cannot be explained by a generally lower threshold for admission in higher prescribing authorities since there is, if anything, a slight increase in admissions for acute uncomplicated infections and a significantly higher rate of admission for tonsillectomy.

Aggregated data: the ecological fallacy

It is possible that patients who suffer the complications in low prescribing areas in fact come from high prescribing doctors within those areas. This is an unlikely explanation since it goes against the limited trial evidence.[14] To assess whether prescribing truly protects against complications in the routine setting, detailed prospective clinical information is needed on an individual basis. Currently, aggregated data which take account of the likely demographic differences between areas are likely to be the best available indicator of whether antibiotics prescribed in everyday practice prevent complications. We have also used the largest dataset available, which enhances the security of the data.

Main findings

Quinsy and mastoiditis. These data suggest that prescribing antibiotics in a routine setting is likely to be associated with fewer admissions with quinsy when controlling for the demographic differences between health authorities. The causal link between prescribing antibiotics and preventing quinsy is supported by the limited trial evidence.[14] Similarly, prescribing antibiotics is likely to be associated with fewer admission with mastoiditis, which supports the conclusions of limited case series in European populations.[21] Assuming that this data can be extrapolated for a large practice of 10 000 prescribing at the average rate for health authorities (0.48 items of penicillin), to save one admission with either quinsy or mastoiditis would require prescribing at the highest rate (0.69) or approximately 2000 extra items per year. Thus to prevent the suffering and inconvenience of one patient would require a dramatic rise in prescribing. This would dramatically increase patient expectation and attendance with respiratory infections — since prescribing increases both belief and reattendance by 40%[22,23] — would probably lead to rapid development of antibiotic resistance,[2-6] and from the current data could overall possibly increase use of secondary care. Thus an overall increase in antibiotic use is probably not sensible or efficient.

If prescribing is not to be increased then it is important to selectively target antibiotics to at-risk individuals. The evidence for tonsillitis suggests that, for unwell individuals with three out of four of the 'Centor' criteria (absence of cough, purulent tonsils, cervical adenopathy, and fever), the risk of quinsy is higher (1:60), compared with individuals who are not unwell (1:400) and that antibiotics may prevent complications.[24,25] Although the 'Centor' criteria are useful, they are limited since they were developed using the throat swab as the criterion. The throat swab cannot distinguish carriage from infection and hence is neither particularly sensitive nor specific (the main problem) for immunological evidence of infection, which better predicts complications.[26] Similarly, for otitis media, children in day care, those with recurrent infections, and bottle-fed children may have poorer outcomes at three months,[27,28] but what predicts poor short-term outcome is unclear. For chest infections, clinical features associated with pneumonia have been documented[29-37] but few are prospective studies based in primary care. Thus we need better evidence of valid clinical scoring methods, or near-patient tests to identify individuals at risk of poor short and long-term outcomes for acute respiratory infections.

Increased prescribing and rates of tonsillectomy. Higher prescribing rates are associated with increased rates of admis-

sion. This is not confounded by socio-demographic variables, since the unadjusted and adjusted estimates are very similar. The explanation is likely to relate to the sequelae of health professional behaviour. Doctors who prescribe more are likely to have significantly higher rates of patient attendance for respiratory illness owing to effect on belief and behaviour[22,23] and prescribing immediately rather than using the delayed approach may increase recurrence rates based on the combined estimates of three trials.[38-40] Thus, with higher attendance for infections and recurrence, the referral rate is likely to be higher. Furthermore, doctors who prescribe more may also have lower thresholds for referral. Whether the higher rates of referral for tonsillectomy in higher prescribing health authorities is appropriate is unclear: the recent Cochrane review concluded that there was too little trial evidence to support the use of tonsillectomy.[41]

Conclusion

These data require confirmation in large prospective cohorts or trials, but suggest that higher antibiotic prescribing is associated with fewer admissions with complications in the routine setting. However, the overall size of the effect is modest and it is difficult to advocate an overall increase in prescribing to prevent complications. Thus there is an urgent need to find better methods of targeting antibiotics to individuals at risk of poor outcome without increasing overall antibiotic use.

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