Can 88% of patients with acute lower respiratory infection all be special?

BACKGROUND

Acute lower respiratory tract infection (LRTI), also referred to as 'acute bronchitis' and 'acute chest infection', remains one of the most common presentations to primary care internationally.[1] Usually defined as an acute cough with at least one of the following, sputum, chest pain, shortness of breath, and/or wheeze,[2] between 52% and 100% (median 88%) of patients are currently prescribed an antibiotic.[3] Using conservative national morbidity survey estimates,[1] LRTI costs the UK NHS an estimated £190 million annually.[4]

Despite good evidence that antibiotics do not reduce the duration or severity of LRTI,[5] they continue to be widely prescribed[3] promoting bacterial resistance to antibiotics.[6] Between 2002 and 2010, the total number of antibiotics dispensed per 1000 population in England increased by an alarming 25%,[7] a statistic that cannot be explained by increasing primary care presentations: consultations for upper and lower RTIs fell by 19% in the same period.[8]

So why is our antibiotic prescribing increasing? There is evidence that a key concern is avoiding under-treatment.[9] None of us wants to be seen to have withheld treatment from a patient who subsequently deteriorates, especially if they are hospitalised. Although rare, it damages doctor–patient relationships, and leads to complaints and medico-legal consequences. However, the rising use of antibiotics and antimicrobial resistance is also of concern, and is now at the top of the Chief Medical Officer (CMO) for England, the Department of Health and the National Institute for Health Research (NIHR) agendas. In March 2013, the CMO highlighted the rise of antimicrobial resistance as a threat to healthcare delivery,[10] in August 2013 the NIHR launched a themed antimicrobial resistance call for research and in September 2013, the Department of Health published the *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018*.[11]

NEW RESEARCH EVIDENCE

This month's *BJGP* includes two articles providing evidence to help improve antibiotic treatment decision making.[12,13] They are both from the humbly named 'GRACE' consortium (www.grace-lrti.org), an internationally respected group

"None of us wants to be seen to have withheld treatment from a patient who subsequently deteriorates"

of primary care researchers who worked with hundreds of GPs and nurses from 12 European nations to conduct high quality research into LRTI in over 3000 adults. A strength of both studies is that LRTI was transparently defined to maximise generalisability: adults (≥18 years) were eligible if presenting to primary care for the first time with acute (≤28 days) cough as the main symptom, and non-infective cause (such as pulmonary embolism or heart failure) was judged very unlikely. Exclusions included suspected community-acquired pneumonia, penicillin allergy, or immunodeficiency. Patients with asthma and chronic obstructive pulmonary disease (COPD) were eligible, and constituted 15% of the final sample.

The article by Moore *et al*[12] is a secondary analysis of a previously published randomised controlled trial (RCT).[14] The largest of its kind, 2061 patients were randomised to amoxicillin 1g or placebo three times daily and asked to complete a validated diary[15] to measure duration and severity of the most common LRTI symptoms. Symptom severity was measured using a scale of zero ('no problem') to six ('as bad as it could be') that included the interim score, three ('moderately bad'). Despite the higher than standard UK treatment dose, the trial demonstrated no difference in overall duration of all symptoms rated 'moderately bad' or worse (≥3) or their severity at days 2–4. Although new or worsening symptoms occurred slightly less frequently in the amoxicillin group (16% versus 19%, number needed to treat = 30), nausea, diarrhoea or rash occurred more frequently (number needed to harm = 23) and there was one anaphylaxis in the amoxicillin group. Three (0.15%) patients needed hospitalisation for cardiovascular or respiratory problems, two in the placebo and one in the amoxicillin group. Figure 1 in the Moore article shows the strength of evidence for the lack of effect on duration of 'moderately bad' or worse symptoms.[12]

But, we hear you say, my patient is special they need antibiotics because they are a smoker/have green phlegm/a more severe illness/chronic lung disease/are going on a family holiday tomorrow/have a vitally important business meeting in Washington DC next week (delete as appropriate). Moore *et al*[12] address 'being-special' by investigating patient subgroups who might differ from the full group, for whom antibiotics may offer extra benefits (or harms). Also referred to as 'looking for interactions', this article reports effects of antibiotics on patient subgroups defined by the presence/absence of factors that are of clinical concern: green phlegm; currently smoking; 'significant past medical history'; longer illness duration prior to consulting; fever at presentation; and 'minor' chest signs (not suggestive of pneumonia).

Although there appear to be some statistically important findings (suggesting patients with significant past medical histories, shorter prior illness duration and those who don't smoke gain from amoxicillin), Moore *et al* conclude that:

'There is no clear evidence of clinically meaningful benefit from antibiotics in subgroups of patients with uncomplicated LRTI …'.[12]

So, why the caution?

STATISTICAL MINI-TUTORIAL

There are three main types of subgroup effects which could be considered as 'interactions':[16] first, treatment effects in both subgroups in the same direction but of different sizes; second, a treatment effect only in one subgroup; and third, treatment leading to harm in one subgroup but benefit in the other. A trial with 80% power to detect a given size of an overall treatment difference would have only 29% power to detect an interaction of the same size, if the subgroups are of equal size.[16] Where the interaction size is smaller, as is often the case in pragmatic trials, or where subgroup size is uneven, the power falls further. Recommendations for subgroup analyses include that significance (*P*-value) of individual subgroups should not be reported,[17] that focus should be on interpretation of the confidence intervals, that the size and direction of the anticipated effects in planned subgroup analyses should be identified before analysis,[17] and that a more conservative *P*-value should be used to take account of multiple testing (known as Bonferroni correction).[18] Here, 18 interaction tests were carried out, so the Bonferroni correction would have lowered the *P*-value for 'significance' from 0.05 to 0.003. Together, the above means this study is likely to be underpowered to detect even large interactions between subgroup and antibiotic use and that only the interaction between past medical history and symptom severity would be deemed unlikely to be due to chance alone.

The second *BJGP* article from the GRACE consortium, by Hamoen *et al*,[13] shows interesting and marked variations

"The main antibiotic trial article suggests patient safety was not improved by using antibiotics — if anything, their use may compromise safety …"

between 12 European nations in the use of symptomatic remedies prior to presentation, including (percentages given for extremes of range): antibiotics (0–26%); antitussives (5–21%); mucolytics (0–30%); expectorants (0–15%); antihistamines (0–18%); inhaled bronchodilators (0–5%); inhaled corticosteroids (0–11%); aspirin and other salicylic acid derivatives (0–19%); paracetamol (4–48%); and NSAIDs (0–15%). These mirror between-nation variations in the use of antibiotics,[19] many without any accompanying evidence of benefit.

CONCLUSIONS

The main antibiotic trial article suggests patient safety was not improved by using antibiotics — if anything, their use may compromise safety — more patients experienced side effects than were prevented from experiencing worsening of their illness, and we already know about the dangers of anaphylaxis and antimicrobial resistance. The caveat is that patients with more severe illness may not have been recruited to the study, and the subgroup analysis suggests patients with 'significant past medical histories' (most of whom had asthma or COPD) may differentially benefit from antibiotics. Therefore, caution needs to be exercised for the more unwell, and we should continue to follow national guidelines

for patients with COPD exacerbations, but most patients with acute chest infections (in whom pneumonia is not suspected and without significant past medical histories) should not receive antibiotics.

Further research is needed to see if there are other 'special' patient subgroups more likely to benefit from antibiotics (for example, those with haemoptysis and infective exacerbation of asthma), and to evaluate if other remedies can safely and effectively replace antibiotics. But given the strength of evidence to date, perhaps we should also ask ourselves if 88% of patients with acute LRTI can all be special?

Alastair D Hay,
Professor of Primary Care and NIHR Research Professor, Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Bristol.

ADDRESS FOR CORRESPONDENCE
Alastair D Hay
Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Clifton, Bristol, BS8 2PS, UK.
E-mail: alastair.hay@bristol.ac.uk

Kate Tilling,
Professor of Medical Statistics, School of Social and Community Medicine, University of Bristol, Bristol.

Provenance
Commissioned; not externally peer reviewed.

Competing interests
The authors have declared no competing interests.

DOI: 10.3399/bjgp14X676636

REFERENCES

1. McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice. Fourth National study 1991–1992.* London: HMSO, 1995.
2. Macfarlane JT, Holmes WF, Macfarlane RM. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. *Br J Gen Pract* 1997; **47(424):** 719–722.
3. Ashworth M, Charlton J, Ballard K, *et al.* Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK practices 1995–2000. *Br J Gen Pract* 2005; **55:** 603–608.
4. Little P, Rumsby K, Kelly J, *et al.* Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *JAMA* 2005; **293(24):** 3029–3035.
5. Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2004; **(4):** CD000245.
6. Costelloe C, Metcalfe C, Lovering A, *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340:** c2096.
7. Hay AD, Costelloe C. Antibiotics for childhood urinary tract infection: can we be smarter? *Br J Gen Pract* 2013; **63(609):** 175–176.
8. Royal College of General Practitioners. Research & Surveillance Centre Weekly Returns Service Annual Report 2011. http://www.rcgp.org.uk/clinical-and-research/~/media/Files/CIRC/Research%20and%20Surveillance%20Centre/RSC%20Annual%20Report%20-%202011/Annual%20Report%202011%20Final%20%282%29/RSC%20Annual%20Report%202011.ashx (accessed 13 Jan 2014).
9. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. *BMJ* 2003; **326:** 138.
10. Davies SC. *Annual Report of the Chief Medical Officer 2011: volume 2.* London: Department of Health, 2013.
11. Department of Health. *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.* London: Department of Health, 2013.
12. Moore M, Stuart B, Coenen S, *et al.* Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups. *Br J Gen Pract* 2014: DOI: 10.3399/bjgp14X677121.
13. Hamoen M, Broekhuizen BDL, Little P, *et al.* Medication use in European primary care patients with lower respiratory tract infection: an observational study. *Br J Gen Pract* 2014: DOI: 10.3399/bjgp14X677130.
14. Little P, Stuart B, Moore M, *et al.* Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13(2):** 123–129.
15. Watson L, Little P, Moore M, *et al.* Validation study of a diary for use in acute lower respiratory tract infection. *Fam Pract* 2001; **18(5):** 553–554.
16. Brookes ST, Whitely E, Egger M, *et al.* Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 2004; **57(3):** 229–236.
17. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005; **365(9454):** 176–186.
18. Wang R, Lagakos SW, Ware JH, *et al.* Statistics in medicine-reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007; **357(21):** 2189–2194.
19. Goossens H, Ferech M, Vander Stichele R, *et al.* Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365(9459):** 579–587.

Editorials

The future shape of primary care

There is no shortage of international policy documents outlining the importance of primary care. But does the reality match up to the rhetoric? This is answered in part in a study by Kringos *et al.*[1] They describe primary care in 31 European countries in terms of investment in primary care, governance, workforce development, access, services delivered, continuity, coordination, comprehensiveness, and GPs' income.

One fundamental, if not surprising observation is that primary care is highly variable. This starts from defining who provides primary care, to whether 'GP' means the same thing in different countries, whether GPs work single-handedly or collaborate with others in multidisciplinary teams, whether they have a gatekeeping role, whether they have a registered list and the range of services that are provided, to working conditions and income. Using a wide range of indicators on the different dimensions, Kringos and colleagues developed a measure of 'strength of primary care', according to which countries such as the UK, Denmark, and Netherlands rank top, while others such as Austria, Cyprus, Greece, Hungary, and Ireland score poorly on care structures considered key for strong primary care. The study provides a great deal of detail to add to previous surveys documenting wide variation between primary care in different countries.[2]

CHALLENGES FOR PRIMARY CARE

In a separate article, the same authors looked at the relationship between strength of primary care countries and the outcomes and the cost of health care provided.[3] They found that countries with strong primary care systems had better health outcomes but, contrary to received wisdom,[4,5] these countries had more expensive healthcare systems relative to national income. However the article suggests no room for complacency in terms of thinking that primary care is necessarily cheaper than specialist care. Nor can we be complacent about primary care producing better health outcomes: Vedsted and Olesen[6] found that countries in which GPs were gatekeepers to specialist care had lower survival for cancer, which suggested that gatekeeping might have 'unexpected serious side effects'. Countries such as France, which are rated medium in terms of primary care, are among the top performers in relation to health outcomes that can be attributed to health care.[7]

"There is increasing recognition that primary care should be organised to take responsibility for whole populations of patients."

So where are we then? There is widespread variation in the way primary care is conceptualised and implemented, and some uncertainties about the costs and effectiveness of primary care. What is clear is that the changing burden of disease vis-à-vis ageing populations requires a different approach to service delivery and components such as continuity and care coordination that are core dimensions of primary care, which have been shown to be effective (to a degree) to meet the needs of those with complex conditions.[8,9] How should we then expect primary care to develop in the future? We address this from two perspectives: how should primary care be organised? And how should it be financed?

FUTURE ORGANISATION OF PRIMARY CARE

There is increasing recognition that primary care should be organised to take responsibility for whole populations of patients. In countries with registered populations GPs take responsibility for screening programmes and increasingly for a wide range of chronic disease management programmes. However, one of the key objectives in extending GPs' population responsibilities in future is to improve the integration of care which is a major priority with our increasingly aged and multimorbid patients. To do this general practice needs to change. GPs increasingly need access to the skills of a multidisciplinary team and to facilities for investigation and treatment. This is at odds with the organisation of general practice in many countries where GPs are self-employed, often working single-handed or in small groups. Recent work describes a number of models which are emerging in the UK and other countries that seek to provide the benefits of organisational scale while preserving the local nature of general practice,[10,11] suggesting design principles for clinical care and organisation of general practice that will be needed to meet the needs of patients in future.[10]

FUTURE FUNDING OF PRIMARY CARE

We also need new models of funding primary care to enable provision of better integrated care. Increasingly, there are moves to try to promote integration of care through so called 'bundled payment systems' which may include payments being made to more than one provider (that is, primary and secondary care) to cover whole episodes of illness, or for implementing care pathways or disease management programmes. Such schemes are now evident in the Netherlands.[12] These schemes recognise that payment systems which encourage multiple providers and give them different incentives are unlikely to provide well coordinated care. Pay-for-performance is also increasingly used in primary care and has spread from the UK to Germany, France, Estonia, Hungary, and Sweden despite limited evidence of its benefits unless used as part of other quality improvement initiatives.[13] Pay-for-performance schemes also have a problem that they tend to prioritise the management of single conditions over integrated care.

A major recent innovation in funding is the potential for primary care to use its population responsibility to take on wider

"... new models of funding primary care to enable provision of better integrated care."