The role of evidence in the decline of antibiotic use for common respiratory infections in primary care

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Antibiotic prescribing in primary care for common respiratory infections increased steadily until the mid 1990s, when the trend reversed noticeably. During the subsequent decade, antibiotic prescribing reduced by up to one-third in some countries. Explanations for this reduction have focused on a decline in the incidence and severity of common respiratory infections, and on the resulting decrease in the number of patients seeking consultation. We argue that evidence from primary-care research had a central role in changing the practice of antibiotic prescribing, and discuss the concern that has arisen among some physicians around this issue. Targeted reductions in antibiotic prescribing constitute a balancing act between individual and societal concerns, pitting the expected gains in preserving the usefulness of an antibiotic against any given reduction in use. There may be unintended consequences for decreasing antibiotic use beyond a certain point without adequate supporting evidence. A new approach to antibiotic prescribing requires comprehensive research to answer why change is necessary, and how that change can be safely implemented. Future policies must move beyond a "one size fits all" mindset if public and provider behaviours are expected to become more congruent with the growing research evidence.

Lancet Infect Dis 2007; 7: 749–56

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Introduction

In the UK, 80% of all antibiotic prescriptions are from primary health-care.[1] Most patients consulting in primary care present with respiratory tract infections,[2] and these conditions are commonly treated with antibiotics.[3] In this Personal View, we examine the changing trends in infectious disease, primary-care consulting behaviour, and antibiotic prescribing. We then explore the influence that primary-care research has had on these trends, and how this research has led not only to fundamental changes in the way infectious diseases are managed, but also to changes in the very structure of primary care in more developed countries. Finally, we consider the consequences of overprescribing or underprescribing antibiotics and how future research can best address the complex challenges that lie ahead.

Overestimating the role of antibiotics in the management of common infections

The 20th century witnessed a pronounced decline in infectious disease mortality. Although not unrelated to Sir Alexander Fleming's discovery of penicillin, this decline was mainly the result of improvements in a number of social determinants of health—for example, diet, housing, and sanitary water.[4–11] Penicillin did, however, revolutionise the management of many serious infectious diseases.[12] Nevertheless, the striking results seen in the treatment of these serious infections led to an overestimation of the overall societal effects of antibiotics.[13] General practitioners (GPs), who had been used to seeing patients die from pneumonia and acute rheumatic fever, saw immediate, profound benefits in their practice. Despite the falling infectious disease morbidity and mortality,[7,9–11] antibiotic consumption continued to rise in more developed countries, with a peak in several countries around 1992–95.[3,14–17] During this peak period, GPs readily saw many "urgent cases" with common infections such as cough, sore throat, and acute ear pain, either in the consulting room or at home. Many of these visits concluded with a prescription for an antibiotic. In the UK, GPs provided emergency out-of-hours cover and visited adults and children with common infections, often during overnight sessions while on-call.

Research evidence from primary care and declining trends in antibiotic prescribing

By 1976, primary-care researchers began challenging the consensus that outcomes in common infections were generally improved by antibiotic treatment. Stott and West[18] published a landmark randomised controlled trial showing that otherwise healthy adults with acute cough and productive or discoloured sputum did not benefit from treatment with tetracycline. Table 1 summarises the meta-analyses of trials of antibiotics from the Cochrane Library for a range of common infections, and shows the marginal benefits from antibiotic treatment for most of these conditions.

By 1995, on the basis of these small effect sizes, researchers claimed that 20–80% of antibiotics used in primary care for common infections were prescribed unnecessarily.[13,26–30] At the same time, there were growing concerns about the influence of antibiotic prescribing in the community on serious resistant infections in hospitals. Policies and standards of practice using these more accurate estimations of the effects of antibiotics (table 1) led to the development of intervention strategies and research projects to reduce antibiotic prescribing.[31] The amount of antibiotics prescribed in primary care declined during 1995–2005 in most more developed countries,[32] including Sweden,[14] England and Wales,[33,34] and the USA.[17,35–38] For example, in the UK during the period 1995–2000, the standardised prescription ratio fell from 101 to 89 per 1000 patients, an annual change of –3·0 (95% CI –3·6 to –2·3).[39]

	Number of trials	Number of patients	Outcome	Risk ratio (95% CI)*	Number needed to treat (95% CI)†	Reference
Common cold	6	1147	Persistence of symptoms	0·89 (0·77–1·04)	..	19
Sore throat	27	12 835	Main benefit of antibiotics seen at day 3	0·68 (0·59–0·79)	6 (4·9–7·0)	20
Sinusitis‡	3	456	Cured or improved	1·26 (0·91–7·94)	..	21
Otitis media in children	8	2287	Pain at 2–7 days	..	15 (11–24)	22
Bronchitis	9	750	General improvement	1·92 (1·15–3·23)	14 (8–50)	23
Conjunctivitis	3	527	Clinical remission (days 2–5)	1·31 (1·11–1·55)	..	24
Laryngitis	2	206	Objective voice scores	No significant benefit	..	25

..=not reported. *Relative risk of benefit listed in the outcome column in those receiving antibiotics relative to those not receiving antibiotics. †Number needed to receive antibiotic treatment for one to achieve the benefit listed in the outcome column. ‡Sinusitis confirmed by radiography or sinus aspirate; treatment with amoxicillin.

Table 1: **Summary of Cochrane reviews of antibiotic use for common infections**

Emerging evidence and the changing organisation of primary care

Acute upper respiratory tract infections were the most common diagnoses in emergency department visits in the USA between 1992 and 2002,[40] with 38–50%[38,41] of patients prescribed an antibiotic; however, these prescriptions were often inappropriate. For example, a retrospective study of 22 million influenza visits to ambulatory clinics and emergency departments in the USA found that 26% of antibiotic prescriptions were inappropriate.[42] Similarly, the most common reason for consulting a GP in the UK was for a respiratory infection,[2] with patients often using out-of-hours services to receive immediate attention.[43–45] The evidence generated from primary-care research, showing that the most common respiratory infections could be safely managed without the need for immediate assessment or antibiotic treatment (table 1), created a safe environment for policymakers and physicians to consider alternative unscheduled care arrangements. Patients requesting urgent consultations for infectious indications were, with increasing frequency, encouraged to engage in self-care.[46] For example, delayed prescribing—when a physician gives a prescription to a patient with the instruction that they should only fill the prescription if symptoms worsen—became a common practice among primary-care physicians.[47–54]

A locally based, practice and home visit-intensive model of care in the UK was considered no longer necessary for common infections, and the sex-standardised consultation rate in general practice for respiratory infections decreased between 1995 and 2000 from 116 per 1000 patients to 68 per 1000 patients, an annual change of –9·5 (–11·3 to –7·8).[39] With fewer consultations for common infections, GPs were able to devote more time to other imperatives—eg, chronic disease management.

Explanations for the decline in use of antibiotics

Three main hypotheses have been offered to explain the decline in antibiotic dispensing in the community, each of which underscores the crucial importance of the role of research evidence from primary care. We suggest that a combination of all three of the following factors is at play.

First, researchers suggest reduction in incidence and severity of common infections. Fleming and colleagues[55] argue that a reduction in the incidence (or severity) of common infections from 1995 to 2000 resulted in a reduction in the use of antibiotics in UK primary care. Increased protection from a wider range of immunisations against respiratory organisms, such as *Streptococcus pneumoniae*, may now be further reducing the frequency and severity of infections.[56]

Second, Ashworth and co-workers[57] suggest that patients are not consulting as often for common infections, resulting in a reduction of prescribing by physicians. Furthermore, patients are being more careful about how they use antibiotics even if they do consult a physician. Since 1997, fewer patients in England have been collecting delayed prescriptions from pharmacies.[50,58]

Third, a reduction in diagnosis could have caused the decline in antibiotic prescribing. Physicians may be using more evidence-based diagnostic processes. Studies in the UK[59] and USA[60] suggest that physicians are diagnosing fewer common infections for which an antibiotic would be the most obvious form of treatment. However, these studies are only able to speculate as to the reasons for the decline in diagnosis.

Has the use of antibiotics reduced too far?

Some physicians fear that reducing consultations and antibiotic treatment for common infections has begun to harm patients by allowing complications caused by these illnesses to increase. For example, a UK-based GP recently wrote that based on his 30 years of experience, he believes that requests by academics and the government to use fewer antibiotics has led to increases in respiratory tract infections and death.[61] To summarise his challenge to researchers: why do patients who get very ill after being denied an antibiotic for an infection by a GP then become better on antibiotics when they are in the hospital?

Just as there were consequences during the past 50 years for increasing the use of antibiotics in the

	Study period	Country	Study design	Patient characteristics	Study observations
Price et al[62]	12-weeks in 1993/94 and 1999/2000	England and Wales	Retrospective analysis of community-based antibiotic prescribing	Lower respiratory tract infections	Antibiotic prescribing for lower respiratory tract infections had fallen by 30% whereas excess pneumonia mortality adjusted for influenza rose by 50·6%
Little et al[63]	1 year, 1997–98	England	Combined hospital admissions and prescribing analysis and cost data	All hospital admissions linked to respiratory tract infections	A weak association was found for increased penicillin dispensing with reduced hospital admissions for peritonsillar abscess
Van Zuijlen et al[64]	1991–98	Ten developed countries	Compared the incidence of acute otitis media	Children 14 years and younger with acute mastoiditis	There was a lower incidence of acute mastoiditis in children under 14 years of age in countries with higher rates of antibiotic prescribing
Sharland et al[58]	1993–2002	UK	Prescription Pricing Authority database for England, IMS UK database, and the Medicines Healthcare Products Regulatory Agency GP database	Children 15 years and younger with quinsy, rheumatic fever, or mastoiditis	Over the study period, the use of antibiotics for children was halved with no increase in hospital admissions for peritonsillar abscess or rheumatic fever, although an increase in mastoiditis and simple mastoidectomy was shown
Simpson et al[65]	September, 1995 and August, 1996	England and Wales	Pneumonia deaths	Patients aged 14–44 years who died from pneumonia	Death from community-acquired pneumonia was identified in 27 young adults. 20 of those patients consulted a GP for their illness, but only nine received antibiotics before admission to a hospital
Dunn et al[66]	1995–97	UK	Retrospective, case-control study using the General Practice Research Database in the UK	Patients with sore throat complication of peritonsillar abscess	Only 192 (32%) of 606 patients with peritonsillar abscess presented following an initial visit for an uncomplicated sore throat. Analysis of those 192 patients who sought initial treatment for sore throat showed there was no evidence that antibiotics prevented peritonsillar abscess
Mainous et al[67]	1996–2003	USA	National Ambulatory Medical Care Survey on antibiotic prescribing for acute bronchitis/cough in ambulatory care and hospitalisation	Adults aged 18–64 years	Over 8 years, data patterns were non-linear, but there appeared to be a weak/moderate connection between more antibiotic prescriptions and fewer hospital admissions

..=not reported. GP=general practitioner.

Table 2: **Studies showing different levels of association between declining use of antibiotics with increases in respiratory tract infection complications**

community without developing a supporting evidence base, there may be unintended consequences for decreasing antibiotic use beyond a certain point without adequate supporting evidence. Studies that have examined the association between antibiotic prescribing levels and serious complications (table 2) have found conflicting results.[62–67] These studies have mostly been cross-sectional, have relied on incomplete data sets, and have not related antibiotic prescribing in individual patients to complications from common infections in those patients. More studies are needed in which the permissions are in place to link individual data on consultations and antibiotic dispensing with individual data on complications and outcomes from common infections in primary care.

Challenges on the front line

Decisions about antibiotic use are not easy for physicians, patients, or policymakers. Many competing factors need to be balanced (panel 1), and physicians are often challenged with pitting the interests of individual patients against larger societal concerns—for example, antibiotic resistance. Furthermore, physicians must do this without an adequate evidence base to support accurate diagnosis and prognosis. Several studies have shown that in the minds of physicians, the needs of individual patients with potential infections generally outweigh the perceived risks of growing bacterial resistance.[68–71]

Raising the threshold for consulting and prescribing, in the absence of a marked decline in the incidence or severity of common infections, will increase the chances of patients losing out on the potential benefits of antibiotic treatment.[72] Dealing with diagnostic

***Panel 1:* Reasons why a physician may or may not prescribe an antibiotic**

Decision to prescribe an antibiotic

- Alleviate symptoms
- Prevent local and suppurative complications
- Prevent transmission
- Prevent admission to hospital
- Demonstrate concern
- Be seen to act
- Give patients benefit of doubt when an antibiotic is requested
- Save time within consultation

Decision not to prescribe an antibiotic

- Reduce resistance in the community
- Avoid exposure to side-effects and adverse reactions
- Save money
- Reduce consultations for similar symptoms in the future

***Panel 2:* How current uncertainties affect physician prescribing decisions**

Limited capacity to differentiate between viral and bacterial infections in practice

Decisions based on physician diagnosis

In Canada, 12% of common infections seen by physicians were likely to be bacterial infections based on guidelines, but physicians determined that 56% were bacterial[73]

Decisions based on diagnostic tests

Studies of C-reactive protein and other diagnostic tests have shown that the use of these tests can still lead to inappropriate prescribing decisions[74-76]

Limited capacity to assess bacterial sensitivity and choose the most appropriate antibiotic

Decisions to use broad-spectrum antibiotics for illnesses usually not treated

The use of broad-spectrum antibiotics rose from 11% to 41% of bronchitis consultations from 1993 to 1999 in the USA.[77] Broad-spectrum antibiotics were chosen for 54% of patients who were prescribed an antibiotic for upper respiratory tract infections[78]

Decisions to use broad-spectrum antibiotics more often

Fluoroquinolones became the most commonly prescribed antibiotics in adults in the USA between 1995 to 2000, increasing in use by 300%.[79] 42% of fluoroquinolone prescriptions were for non-approved diagnoses

Limited ability to predict outcomes of treatment/no treatment decisions for common infections

Predicting sore throat outcomes

In diagnosing sore throat, physicians are unsure of the need for antibiotics, but use of a clinical scoring system has been shown to have reasonable sensitivity and specificity for predicting streptococcal infection and to safely reduce antibiotic prescriptions by 50%[80]

Predicting sinusitis outcomes

In diagnosing sinusitis, physicians were unsure of the need for antibiotics, but a systematic review has identified the clinical features that are most likely to be associated with a computed tomography or sinus aspirate diagnosis[21]

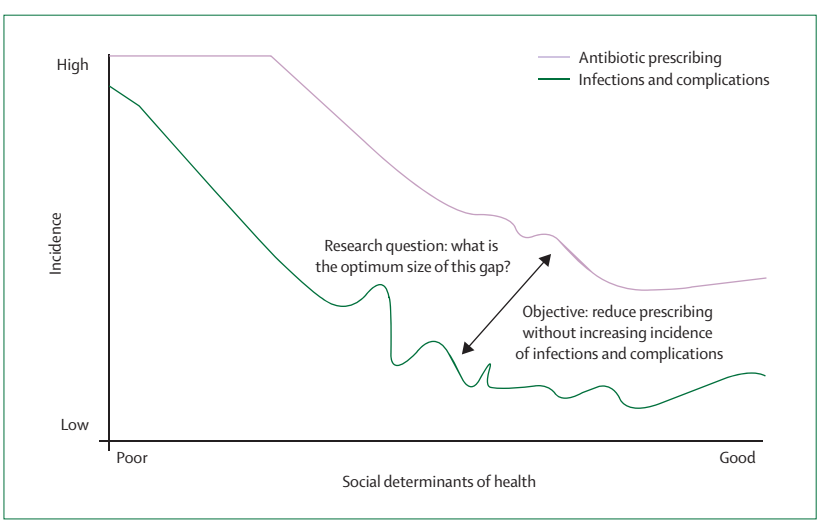

***Figure*: Relating common infection and antibiotic prescribing trends to a primary-care research agenda for common infections**

uncertainty is a key challenge for researchers in this area. Panel 2 highlights some of the advances that primary-care researchers have been making in this regard. Larger studies are now needed, which enable the integration of clinical prediction rules with better near-patient diagnostics when appropriate. The ultimate goal would be to develop feasible tools for diagnostic and prescribing decisions that rapidly combine information about social and demographic factors, clinical history, host genetic factors influencing immunological response, and bacterial characteristics (eg, virulence and resistance factor expression) to successfully target antibiotics only at those who are most likely to receive meaningful benefit.

Choosing targets for reductions in antibiotic use

There is considerable variation in prescribing rates between countries and between individual practices within countries. For example, in 2002, substantially more patients in the UK were prescribed antibiotics compared with the Netherlands (unpublished data, Welsh Common Infections Study Group, Cardiff University, Cardiff, UK). However, should all practices strive to prescribe at the levels achieved in the Netherlands, currently enjoying the lowest rates of antibiotic prescribing and resistant bacteria?[14] Is observational and experimental evidence derived, for example, from the Netherlands or affluent parts of the UK applicable to other countries and poorer regions in the UK? Making the assumption that prescribing targets should be the same in every country and indeed in every general practice risks falling foul of the so-called spectrum bias—eg, when assumptions are made about the performance of a diagnostic test or a treatment effect based on evaluations in settings that are different to the one where the test or treatment is to be used. Social determinants of health will vary considerably between and within countries;[4,5] therefore, we cannot assume that adjusting the level of antibiotic use can balance the infection levels between countries.

Several years ago, researchers asked the question: by how much must antibiotic use be reduced, by 10–50%?[81] To our knowledge, this question cannot yet be answered either at the national or individual physician levels. The figure illustrates the conceptual difficulties in answering this question. The figure shows the decline in infections, complications, and antibiotic use that occur with improvements in the socioeconomic determinants of health, and the gap between the level of infection and level of antibiotic prescribing.

Reducing antibiotic use in the community without subsequently increasing incidence and complications of infections is a desirable goal. However, continuous monitoring of the incidence of infections, complications, resistance, and antibiotic dispensing is essential.[82] Ideally, monitoring the severity of patients' infections should also be done to examine the influence of changes in help-seeking

behaviour. The increase in extended broad-spectrum beta-lactamase producing *Escherichia coli*[83] and the emergence of community-acquired meticillin-resistant *Staphylococcus aureus* are examples of how bacteria can rapidly evolve. The severity of resistant infections has the potential to substantially undermine public confidence in the delayed prescribing approach often adopted in primary care. Ongoing monitoring of infections and their complications is needed to ensure that we identify and respond to such changes early; mechanisms to provide local feedback must be in place so that physicians can make prescribing decisions using information relevant to their local population.

Some experts have suggested that reducing antibiotic prescribing is unlikely to lead to major reductions in antibiotic resistance because acquisition of resistance determinants by bacteria might have less impact on microbial fitness than previously thought.[84–86] However, there is growing evidence to suggest that reductions in antibiotic use do achieve reductions in antibiotic resistance in the community.[87–92] At a country level, a decrease in macrolide use was associated with a decline in isolates of resistant *Streptococcus pyogenes* in Japan[93] and Finland.[87] Clonality, however, may have played a part.[88,89] In Iceland[90] and France,[91] the prevalence of resistant pneumococcal isolates fell after the reduction of antibiotic prescribing for children. In a 7-year study in the UK, we have shown for the first time that reduced antibiotic prescribing at the level of general practice is associated with reduced levels of antibiotic resistance in samples submitted for laboratory analysis from the local practice population.[92] But could reducing the use of one class of antibiotic influence resistance to another? Could reduced antibiotic use in one patient affect his or her subsequent risk of acquiring a resistant infection over time?[94] Having better answers to these questions will influence the priority given to reductions in prescribing, but for now, these reductions ultimately lie within each interaction between the patient and physician.[82,95,96]

Changing prescribing behaviour

There is no universal intervention that will work in changing prescriber behaviour.[97] Some infections require interventions to reduce antibiotic prescribing more than others,[98,99] and high prescribers may require different types of interventions to low prescribers.[100] Standardised messages provide a disservice to physicians who have already reduced use as much as they feel is safe. The barriers to change are variable and often context dependent, and interventions need to take this into account.[101] From social learning theory comes the crucial distinction between outcome and efficacy expectations.[102,103] From research on theory of planned behaviour[104,105] comes a similar conceptual distinction between beliefs about consequences and beliefs about the ability to exert control over change.[106] Taken together, these theories and associated research suggest that behavioural change will be more likely to occur if an intervention addresses the "why" (ie, the importance of change, outcome expectations, and beliefs about consequences) and the "how" (ie, confidence in making changes, self-efficacy, and beliefs about control). Individuals, regions, and countries can use this thinking to focus discussions on topics that are most applicable to their circumstances. Patients, physicians, and policymakers can then have a common language to compare their beliefs about what they want to achieve and how they are going to achieve it.

Search strategy and selection criteria

Data for this Personal View were identified by searches of Medline, PsycINFO, Google Scholar, the Cochrane library, and references from relevant books, articles, and reports, including the files collected by the authors. Literature search terms included "determinants of health", "common infections", "antibiotics", "upper respiratory tract infections", "cough", "sore throat", "trends", "primary care", "resistant", "prescribing", and "developed countries". Only English language articles were used from developed countries, including the UK, USA, Canada, Sweden, Germany, France, and others. An emphasis was placed on data from the UK. No date restrictions were set in these searches.

Conclusions

Antibiotics can be life-saving drugs, but their overuse may lead us back to a time when many serious infections could not be treated.[107,108] Primary-care research has identified the limited benefits that antibiotics have for otherwise healthy people with common respiratory tract infections. This research has led to fundamental changes in the clinical management of these conditions and has influenced the organisation of primary health-care delivery, resulting in reduced antibiotic prescribing. Research from primary care has also generated insights into the complex influences on antibiotic prescribing trends, explored possible detrimental consequences of reductions in antibiotic prescribing, and has started to provide physicians with tools to enable further safe reductions in prescribing.

However, organisational change in primary care needs to occur if we are to improve patient outcomes and further reduce antibiotic use. Large-scale analyses at the level of the individual patient are also urgently needed. Large clinical trials will need to be done with sufficient power for subgroup analysis to provide information about who will benefit from treatment and further testing, how much they will benefit, and for whom self-care can safely be promoted. Studies will also need to determine the best ways of sharing new developments with patients so that physicians can increasingly involve them in the decision-making process. Patients move between primary, secondary, and tertiary care, as does antimicrobial resistance; thus the research agenda should increasingly link these arenas of care.

The challenge of managing common infections is an exciting process because it links developments at the level of biomolecular/genomics with clinical observations, treatment and diagnostic studies, integrated with essential contributions from behavioural, social. and health economic sciences. This research must be turned into policy and ultimately lend to a reprioritising of scarce clinical resources during the next decade of rapid reconfiguration in health.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
JLC was funded by an Academic Visitor's scholarship from the Department of General Practice, Cardiff University, Cardiff, UK, and a Canadian Institutes of Health Research/TIPPS Network Post-Doctoral fellowship.

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