Antibiotic Overuse: The Influence of Social Norms

The McDonnell Norms Group

Since the introduction of penicillin in the 1940s, antibiotics ("antibiotics" refers to antibacterial and antifungal drugs) have become ubiquitous. Many infectious diseases that used to pose immediate threats to human life are now readily treated.

This widespread use of antibiotics has led to at least two undesirable consequences. One consequence includes unpleasant and occasionally lethal side effects resulting from changes in the normal microbial flora. For example, many women experience vaginal yeast overgrowth consequent to treatment of respiratory and urinary infections with conventional antibiotics. A more serious problem is the recent epidemic of antibiotic-associated intestinal infections caused by *Clostridium difficile*, which are becoming progressively more difficult to treat, can sometimes require surgical removal of the colon, and in some cases, lead to death.[1] This previously rare toxin-producing organism, now the most frequent enteric pathogen in the developed world, is able to proliferate to clinically problematic levels as a result of the disturbance of the ecological balance of the microbes of the colon.

An undesirable consequence often reported on in news stories and much discussed in health care policy forums is the emergence of bacterial resistance: the evolution and spread of pathogenic strains that have lost susceptibility to the treating drugs. With the introduction of each new antibiotic, the biologic forces of random mutation and natural selection have led to the appearance of resistant strains that are sustained by continued use of the drugs. New strains of bacteria resistant to multiple classes of antibiotics have increased the risks of morbidity and mortality from hospital-acquired infections, resulting in correspondingly longer hospitals stays and higher treatment costs.[2] The appearance and persistence of resistant organisms has led to an arms race between medicinal chemistry and evolution: a never-ending need to develop and bring to market costlier new antibiotics to treat progressively more resistant infections.[3]

In the past, the problem of resistance was thought to be largely confined to hospitals and nursing homes. Recently, the proportion of community-acquired infections with bacteria resistant to conventional antibiotics has steadily increased.[4] In addition, longer life expectancies and the expansion of chronic care facilities have resulted in a new group of patients at risk of health care-associated infection, with rates between those of the community and of the hospital. The cost of treating these resistant infections has also increased, both in hospital and outpatient settings.[5]

Two perspectives

Public health officers and epidemiologists recognize that the phenomenon of resistance is ecologic, so it is affected by behaviors and events remote in time and in distance.[6,7] For example, when antibiotics are administered to farm animals, the antibiotics themselves and the resistant bacteria for which they select may enter the food webs.[8] This entry may be direct, through milk and meat, or indirect, through runoff that contaminates the water supply. Resistant bacteria evolving in farm animals can spread to humans, and resistant genes can spread to bacteria responsible for human disease. In clinical settings, aggressive use of broad-spectrum antibiotics can favor the rapid emergence of resistant organisms that can spread within and between health care organizations. Although the use of antibiotics in each of these settings is well intentioned, at least some of the antibiotic use comes about as a response to choices made concerning farm management (animal overcrowding) and inconsistencies in health care hygiene (failure to properly hand wash).

Local practices can quickly create regional challenges. Modern transportation systems convey asymptomatic carriers of resistant organisms. They travel in confined spaces that favor transmission. Livestock transport by truck and train is common. Health care systems routinely transport infected patients among nursing homes, community hospitals, and regional centers.[9] Although the relative contribution of transportation to the overall level of drug resistance is debated, there is surely some effect.

The expansion of resistance is viewed differently by front-line clinicians. Doctors grapple with the problem in the context of caring for individual patients, where resistance is viewed as a threat to therapeutic success. Physicians

Competing Interests Declared: None.

This work was made possible by generous support from the James S McDonnell Foundation, St Louis, MO.

Members of the McDonnell Norms Group are listed in the Appendix.

Received December 29, 2007; Revised January 28 2008; Accepted February 26, 2008.

Correspondence address: Timothy G Buchman, PhD, MD, Washington University in St. Louis, 660 South Euclid Ave, Mailstop 8109, St Louis, MO 63110. email: buchman@wustl.edu

ISSN 1072-7515/08/$34.00
doi:10.1016/j.jamcollsurg.2008.02.035

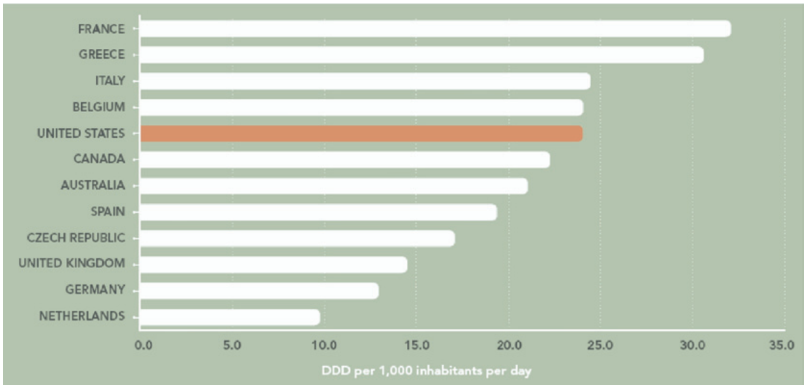

Figure 1. Antibiotic prescribing in the United States and other countries. DDD is an abbreviation for defined daily dose, which is the assumed average maintenance dose per day for a drug used for its main indication in adults. This figure aggregates all DDDs for drugs used mainly as antibiotics. (From: Laxminarayan R, Malani A. Extending the cure: policy responses to the growing threat of antibiotic resistance. Washington DC: Resources for the Future; 2007, with permission). Data sources: United States and Canada: (McManus P, Hammond ML, Whicker SD, et al. Antibiotic use in the Australian community, 1990 to 1995. Med J Aust 1997;167: 124–127; Australia: National Prescribing Service. Antibiotic prescribing is increasingly judicious. National Prescribing Service Newsletter 2005;40(June). Available at: http://www.nps.org.au/resources/NPS_News/news40/news40.pdf. Accessed March 27, 2008; European countries: Goossens H, Ferech M, et al. European surveillance of antibiotic consumption (ESAC) interactive database. Available at: http://www.esac.ua.ac.be. Accessed March 27, 2008.

perceive their primary obligation to be to the individual patient and not to the commons. So if there is even the possibility of the patient being exposed to (prophylaxis) or being infected with (treatment) a resistant organism, the physician is obligated to select and prescribe an antibiotic that is likely to be effective against the possibly resistant strain. This, in turn, leads to ongoing selection for even higher and broader levels of resistance.[10]

Although physicians generally believe that their prescribing of antibiotics is appropriate in the contexts of their personal clinical practices and of their care of individual patients, there is a perception that a significant proportion of all antibiotics are prescribed inappropriately in the United States and other countries including Canada,[11] France,[12] England,[13] and the Netherlands[14] (although underprescribing is also an issue there[15]). Antibiotics are often prescribed for illnesses such as colds, bronchitis, and related upper respiratory tract infections caused by viruses that will not respond to the antibiotic drugs. Although the frequency of inappropriate prescribing in the United States has declined somewhat, it remains high, especially when compared with that in other countries (Fig. 1). Ominously, the proportion of prescriptions for broad-spectrum antibiotics has been increasing.[16-18] This trend toward broad-spectrum prescribing holds regardless of the type of infection or indication for antibiotic treatment (Fig. 2). Making matters worse, resistance genes that have evolved in one group of bacteria can spread to distantly related bacteria through horizontal gene transfer.[19]

Resistance: inevitability and mitigation

Resistance is an inevitable consequence of antibiotic use. The benefits of antibiotic use to society are so great—reduction of individual illness and of infection transmission—that some level of evolved resistance is both tolerable and accepted as a social cost. The concern lies with the rate at which resistant strains of bacteria are emerging, and with the human behaviors that foster faster resistance. Intuition, mathematical models, and empiric observations predict and provide evidence that the rate at which resistance will evolve in a community or hospital is directly related to the magnitude of antibiotic use. It is not by chance that the frequency of antibiotic-resistant bacteria among countries is proportional to their relative rates of antibiotic use.[20,21]

Judicious antibiotic use delays the emergence of resistance.[22] Whether reversing already excessive use reduces resistance is debatable. Two uncontrolled studies are often cited to justify efforts to modify current overprescribing of antibiotics. For example, a reduction in use of the macrolide class of antibiotics (2.4 to 1.38 defined daily doses per 1,000 inhabitants between 1991 and 1996) in Finland was associated with a decline in erythromycin resistance among Group A streptococci from 16.5% in 1992 to 8.6% in 1996.[23] In Iceland, a 30% reduction in use of cotrimox-

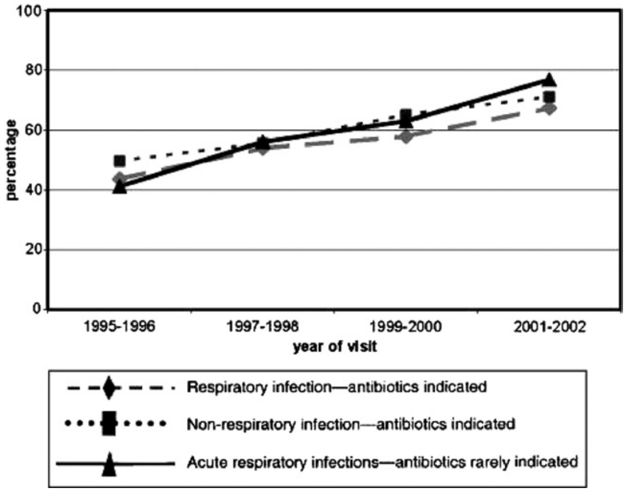

Figure 2. Trends in broad spectrum antibiotic prescribing in the United States by diagnostic category. Irrespective of the validity of the indication, caregivers increasingly select broad-spectrum antibiotics. (From: Roumie CL, Halasa NB, Grijalva CG, et al. Trends in antibiotic prescribing for adults in the United States–1995 to 2002. J Gen Intern Med 2005;20:697–702, with permission).

azole and the macrolides was associated with 10% reduction in resistance to penicillin in *S. pneumoniae*. In contrast, others have failed to demonstrate meaningful reductions in resistance despite seeming success at limiting antibiotic use.[24,25] Several factors, including duration and extent of reduction, fitness cost, lack of substitution, or continuing selection by other drugs may play roles in determining whether reduction in use can reverse established patterns of resistance and reverse the virulence of the resistant strains. Even if decreased use does not result in decreased resistance, it can at least be expected to slow the rise of resistance, which is a worthwhile goal in itself.

Externalities: secondary impacts of antibiotic use

Despite growing awareness of the consequences of overuse, efforts to decrease antibiotic use have generally been unsuccessful. To counter the overprescribing behavior, it is necessary to understand and evaluate the context in which the behavior occurs. The concept of "externalities" (the costs or benefits accruing to those not involved in the primary transaction) offers a useful analytic framework. In the context of antibiotic prescribing, externality refers to the secondary impact on persons and on the environment that occurs outside the prescriber-patient relationship consequent to the treatment.[26]

Neither prescribers nor patients appear to have a sufficiently strong incentive to care about the impact of their immediate use of antibiotics on others. As a consequence, the prescriber-patient dyad uses antibiotics to a greater extent than if the dyad were to bear the full costs of resistance. In this respect, antibiotic resistance is like pollution in that production and dispersion of waste into the environment by individuals have so little immediately perceptible effect that in the absence of external regulation, the behavior continues.[27]

There are at least two potential explanations for this apparent insensitivity to the consequences of excessive antibiotic use, and they are not mutually exclusive. One is that the action and undesirable consequence are so widely separated in time that their relationship is unrecognized or unacknowledged. Another possibility is that individuals acting in "rational" self-interest understand that they alone cannot change the problem of resistance, so any chance of a modest benefit from antibiotic use outweighs the negligible contribution that the individual could make to the common good by refraining from use.

Externalities are necessary, but by themselves are insufficient to explain overuse. For example, geopolitics and economics are often invoked to explain country-specific differences in antibiotic use and resistance patterns. Scandinavian countries have much lower levels of antibiotic prescribing (without any noticeable difference in outcomes) and also lower levels of resistance. But the fact that Scandinavian countries have a single-payer system, unlike that in the United States, is not a sufficient explanation; other European countries (such as France and Belgium) also have single-payer systems, yet have levels of total antibiotic use and broad-spectrum antibiotic use even higher than that in the United States (Figs. 1 and 3). Here, we suggest that a different and underappreciated force may contribute to the variability in antibiotic prescribing—the force of social norms.

Norms: definition and roles

Social norms refer to the rules that govern ordinary and noncontractual interactions among members of a community. Such norms are so widespread that they are often imperceptible. Familiar examples include which hand is used in a handshake, how close it is appropriate to stand to another person, and what attire to wear to a business meeting. Once established, norms can be hard to change, even if the norms are useless or counterproductive. Until quite recently, no serious business meeting convened without neckties, even though ties serve no function. Similarly, smoking in restaurants was considered acceptable, even though tobacco smoke imposed external costs on other patrons. Norms can change in response to a number of factors that collectively focus on improving the general environment. No-necktie casual Fridays have become commonplace as employers acknowledge that their employees want to work in a more comfortable environment as the weekend approaches. Similarly, greater recognition of the

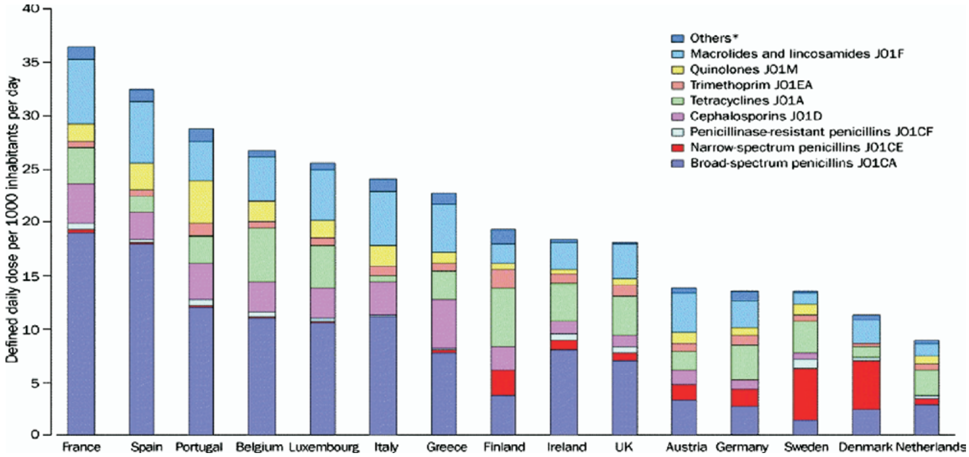

Figure 3. Drug prescribing by antibiotic class in Europe. The classification displayed is the Anatomic Therapeutic Chemical classification. In this classification system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacologic, and therapeutic properties. Drugs are classified in groups at five different levels. The drugs are divided into 14 main groups (1st level), with one pharmacologic/therapeutic subgroup (2nd level). The 3rd and 4th levels are chemical/pharmacologic/therapeutic subgroups, and the 5th level is the chemical substance. The 2nd, 3rd, and 4th levels are often used to identify pharmacologic subgroups when that is considered more appropriate than therapeutic or chemical subgroups. J refers to antiinfectives for systemic use, 01 refers to antibacterials for systemic use, A. . .M refers to the particular class of antibiotics, and the 5th level is used to discriminate within class, eg, the spectra of the various penicillins. DDD, defined daily dose. (From: Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851–1853, with permission).

health risks of smoking resulted in regulation of smoking in public places.[28,29] In some instances, the change in norms even preceded implementation of the stricter regulation.[30]

In the context of antibiotics, social norms govern the transactions patients and doctors expect to occur, for example, during an office visit. Social norms also shape the expected interactions between clinicians in hospital settings. From the physician's perspective, there are strong incentives to balance clinical appropriateness against perceived patient satisfaction.[31] From the patient's perspective, the desire to get better may be linked with an erroneous preconception that the best (fastest, most complete) response is achieved with help from antibiotics. Having a norm serves an important purpose in health care. Competing priorities give rise to multiple equilibria in clinical interactions, and the existence of a norm (in medical parlance, the norm is labeled "standard care") streamlines the process of arriving at a single focal solution.[32]

Clinical examples

A common office situation involves urgent ambulatory pediatric care. The urgency presented by parents with crying children means that pediatricians frequently find it easiest to focus on a resolution of the visit that involves an antibiotic prescription, whether or not antibiotics are required to address an infection. The prescription serves an important psychological role in acknowledging the child's (and parents') suffering and validating the decision to seek medical attention. It signals the end to the office visit, providing a solution that coordinates expectations between parents and the physician. In fact, physicians can perceive a parental desire for antibiotics even if none is expressed.[33] An alternative way to address the expectation is to delay an antibiotic prescription in the promise of one if the child is not better after a few days. This strategy has been used effectively in the United Kingdom to reduce antibiotic prescribing since the early 1990s.[34] But the strategy adds costs to the parents, who often must miss work to bring the child to the physician once (let alone twice). Indeed, this may be a major reason for the perceived pressure to leave the office with a prescription in hand. One way to work around this barrier is to provide a "delayed-fill" prescription, with explicit instructions for when to use it. This mechanism provides a sense of security and control because the parent or patient is in a position to fill the prescription without further inconvenience should symptoms escalate or not resolve.

Underscoring the importance of social norms in antibiotic prescribing is the US experience with acute otitis media. Despite the evidence that initial observation without antibiotics is safe and effective, no national professional body of emergency medicine has yet recognized or endorsed the evidence. The community of pediatricians with-held endorsement until 2004. As a consequence, review of the national trends in emergency department antibiotic prescribing for otitis media demonstrates a small but steady increase from 1994 to 2005, culminating with more than 90% of children receiving antibiotics at the time of initial presentation.[35] Once again, social norms trump evidence.

The inpatient environment also has increased the use of broad-spectrum antibiotics. For example, a frequent hospital situation involves the now-common prescribing of vancomycin to patients who are at risk for infection with a gram-positive organism such as *Staphylococcus aureus*. Although the pervasive prescribing behavior predisposes to the increased prevalence of vancomycin-resistant enterococci, widespread resistance of *Staphylococcus aureus* to more traditional anti-Staphylococcal drugs such as methicillin has created a norm of vancomycin as the reflexive choice antibiotic when infection with this organism is suspected.[36] So ordering one of the older antistaphylococcal drugs is increasingly perceived as a breach of the new norm. In this way, vancomycin's role as an empiric choice for both prophylaxis against and treatment of staphylococcal infections is not only legitimized, but actually is now embedded in practice patterns as a standard of care. Yet data suggest that reflexive use of vancomycin is counterproductive, as in the failure of vancomycin prophylaxis in a methicillin-resistant *Staphylococcus aureus*-dense cardiac surgical environment.[37] Unfortunately, rather than revising the empiric choice to more traditional antibiotics, clinicians are increasingly turning to even more exotic drugs such as linezolid, often without microbiologic justification.[38]

Both of these clinical examples reflect a balance among cost, risk, and benefit. For patients (and families), the cost of the prescription is frequently dwarfed by the cost of the doctor visit in both money and time. The risk of taking the prescribed antibiotic is thought to be small, and the benefit of the antibiotic is believed to exceed the risk. From the physician's perspective, there is little risk in prescribing an antibiotic and less in prescribing a broad-spectrum antibiotic. Failure to prescribe may lead to patient dissatisfaction or worse. From an economic perspective, selfish preferences and individual maximization of benefit provide a simple explanation for overprescribing behaviors.

Behavioral inertia

Established norms allow undesirable practices to persist even in the face of a variety of disincentives. For instance, hog and poultry farmers continue to use antibiotics even though the returns from antibiotic use for growth promotion are not worth the cost.[39] Antibiotic-containing bowel cleansing regimens are still prescribed before operations even though evidence suggests no benefit and the possibility of harm. Learned practices, especially those handed down from professor to student, resist change even when introspection suggests no rationale for the practice and when there is adequate information to suggest an better alternative. Often, powerful economic signals must be used to alter strongly embedded practices, such as when a large corporate entity specifies that a product or service must meet a new specification. Imagine if, in response to consumer demand, a major fast food chain announced that it would purchase meat only from animals raised without antibiotics.[40] Such a signal could provide a greater impetus for lowering antibiotic use than regulatory action or a tax on antibiotics.

A key barrier to changing practice is incomplete knowledge of optimal care. For example, a physician's recommendation of the duration of antibiotic treatment is somewhat arbitrary and often driven by an episode in which another patient relapsed after cessation of therapy. Prescribing behavior driven by anecdotal experience leads to lengthier recommended courses. Patients are exhorted to "complete the course"—that is, to finish the bottle of antibiotics—even if symptoms have fully resolved. The scientific foundation for such recommendations is much weaker than is commonly appreciated.[41]

How are antibiotic prescribing norms enforced?

Norms with respect to antibiotic prescribing are enforced in the United States through two complementary mechanisms, namely, shared expectations and censure. For example, there is a shared expectation by patients that a cold that is symptomatic enough to require a doctor visit warrants prescription medicine. It makes little difference to the patient that scientific consensus is to the contrary, so antibiotics continue to be prescribed inappropriately. This is backed up by the threat of censure or punishment for norms violation. The pediatrician who declines to give an antibiotic to an exhausted mother with a screaming child risks losing a patient and considerable good will. Such norms are cultural and local, as evidenced by the phrase *community standard*. In Scandinavian countries, the prescribing norm is different, and switching physicians is difficult.[42,43] Going to another doctor may not increase the likelihood of getting an antibiotic prescription.

How do clinical antibiotic prescribing norms become established?

Norms typically grow through accumulation of precedent. In medicine, accumulation of precedent is further enforced by the teaching structure. Trainees are expected to follow their teaching physicians' preferences. Failure to follow the preference of a more senior attending physician was classified by Bosk[44] as a quasi-normative error and observed to

Table 1. Drivers of Antibiotic Overuse

	Patient	Physician	Society
Belief	Acute illnesses are treated effectively with antibiotics.	Specific diagnosis of infectious cause cannot be made with precision during a brief encounter.	Excess antibiotic use leads to emergence and expansion of resistance. Adverse effects on the commons are uncertain.
Expectation	A visit to the physician leads to an antibiotic prescription. (In less-developed systems, the physician is bypassed, and antibiotics are purchased over-the-counter.)	Patients value and expect a prescription to signal the end of a visit.	Physicians and patients will make "correct" decisions about use of antibiotics.
Incentives	Antibiotics are inexpensive, and recovery generally follows their use.	It is better to give an antibiotic that is not needed than withhold one from a patient who could benefit. Failure to prescribe risks patient well-being and accusations of negligence.	Antibiotics that reduce the burden of infectious illness are "worth the cost" of resistance.

be subject to rebuke and harsh punishment, even in the face of high-quality evidence suggesting a different course of action. Bosk pointed out that repetition of such quasi-normative errors can result in dismissal from training programs. Small wonder, then, that trainees heed eminence over evidence. Trainees not only assimilate and practice the desired behaviors but also promulgate those behaviors to their own juniors.

In the realm of antibiotic prescribing, physicians fear the sin of omission—failure to treat a treatable infection—much more than they fear an adverse consequence of commission. There is a widespread and largely correct perception that antibiotics are inherently safe drugs, meaning that there is little risk to taking an antibiotic even if there is no infection. Failure to treat a treatable infection in a timely fashion quickly becomes apparent to patient, physician, and peers. The omission is nearly unpardonable. Because patients who do not need antibiotics typically recover without apparent ill effects of the unnecessary prescription, it is not surprising that excess prescribing has become an embedded behavior. Conversely, the adverse consequences of direct toxicity, drug interaction, replacement of normal flora, and transfer of resistant organisms are often so remote in time that the prescribing physician and patient are unaware that inappropriate prescribing of antibiotics is the root cause. Even for the immediate adverse consequences such as allergic reactions, there is commonly an acceptance of these as evidence of the potency of the agents used.

Cementing the pattern are patients' expectations, generated by repeated experiences that a trip to the doctor with remotely infectious symptomatology results in an antibiotic prescription, which further reinforce the overprescribing behavior. It is difficult for physicians to argue against a patient whose earlier and similar symptoms were "cured" by an antibiotic course. Failure to prescribe is seen by many patients as a failure to treat, and can be a reason to seek an alternative physician who is "more responsive" to perceived needs.

Patient, physician, and society underlie current norms

Antibiotic prescribing norms collect and reflect complementary beliefs, expectations, and incentives among three primary parties: patients, physicians, and society (Table 1). At their core is the human need to respond with action when illness strikes.

We have already discussed how medical teaching and experience reinforce prescribing behavior. In this section, we explore why the normative behavior has been refractory to change despite overwhelming evidence that it must change.

The physician-patient relationship

At the core of the behavior is the physician-patient relationship. Since Hippocrates—who was a physician and not a public health officer—physicians have been trained to act on behalf of their patients as individuals, even when that action may be in conflict with the general good of society. So physicians frequently recommend treatments that "might work" in an individual patient despite evidence that the particular treatment is costly, ineffective, or even potentially harmful when considered in the context of a large population. As long as the physician and patient believe that the balance between potential benefit and risk within that unique physician-patient relationship favors prescription, an antibiotic will be prescribed. What might be good for society, for a third-party payor, for public health, for the microbial world, for the patient in the next bed who is the responsibility of another physician, etc, is largely irrelevant to the decision to recommend or withhold an antibiotic.

This explains, at least in part, why actions directed either at physicians or at patients have been generally ineffective: both members of the doctor-patient dyad must agree that the proposed actions are appropriate. It is harder to explain, however, why simple and appropriate interventions aimed at both groups have not gained traction. An example is the "cold care kit," a convenience package of nonprescription remedies and amenities aimed at relieving the symptoms of viral upper respiratory infections. The packs were designed so that the physician had something to give that reflected best practice and also to satisfy patients' need to have received something from their health care provider. Such kits have been shown to reduce antibiotic prescribing. There is no evidence that patients are reluctant to accept the kits as appropriate treatment. Yet they have not become popular.

Different incentives

A plausible explanation for excess antibiotic prescribing is that physicians and health care organizations are responding to different incentives. One such incentive can be found in the guidelines for managing upper respiratory tract infection, published by the American College of Chest Physicians, which state that a viral upper respiratory tract infection is indistinguishable from acute bacterial sinusitis in the early stages, and that "Clinical judgment is required whether to institute antibiotic therapy."[45] From the perspective of a prescribing physician facing an indeterminate clinical situation, the safe judgment most often leads to prescription. Another incentive can be found in quality improvement initiatives that focus on early antibiotic therapy for patients with lower respiratory tract infections, especially community-acquired pneumonia. Medicare's Product Quality Research Initiative (pay for performance) program focuses on timely administration of antibiotics for this infectious disease without penalty for inappropriate administration of antibiotics for viral upper respiratory tract diseases. As a consequence, most emergency departments now initiate antibiotic therapy on every patient who might have a respiratory infection without regard to specific location or to probability that a susceptible bacterium is the causative agent. Once the antibiotic treatment is initiated, it becomes difficult to stop because the individual patient improves whether the disease is self-limited (as in the common case of the viral upper respiratory infection) or is actually responding to the treatment, and because of the widely held belief that antibiotic courses must be finished under all circumstances.

Unfortunately, new and conflicting incentives continue to appear. For example, responding to overcrowded emergency departments and recognizing a marketing opportunity, some pharmacies are facilitating development of adjacent and in-store, nurse practitioner-staffed, walk-in clinics. These low acuity facilities are intended to treat common complaints such as the cough and runny nose associated with a viral upper respiratory infection. Having such economic and social ties between pharmacies and clinics might well increase the incentive of clinicians to write unnecessary prescriptions. A recent estimate suggested that each visit to a pharmacy-associated clinic results (on average) in one prescription.[46] Many of these are likely antibiotics. The proliferation of storefront clinics is seen as socially desirable; care can be delivered at lower cost while decompressing emergency facilities. Patients see the development of storefront clinics as efficient and user friendly. Pharmacies are leveraging the opportunity to augment business.

Toward better norms: guidelines and aligned incentives

Guidelines for antimicrobial therapy have become a major focus of professional societies interested in infectious disease. The benefits of these guidelines are primarily to provide decision-makers —be they practitioners, pharmacists, or formulary committees—with expert recommendations operationalized as structured decision trees. Given the heterogeneity of drug selection mechanisms in place, order form-based decision trees outlining first-line selections and preferred duration provide a minimum level of administrative control over the selection of specific agents.

Application of many of these guidelines has been highly variable because the guidelines leave considerable discretion to the individual practicing physician and allow selection of almost any agent the prescriber desires under the guise of "clinical judgment." Of greater concern, professional guidelines concerning antibiotic therapy do not specifically limit decisions to treat, nor do they emphasize limiting therapy. Guidelines are recommendations to be considered and not protocols that must be followed.[47] If the key issue is preventing the very first dose of unneeded therapy, the current emphasis on choosing the "right" antibiotic is misplaced.

In addition, antimicrobial guidelines separate out and address only one phase of the disease management process. Specific disease-based guidance, including suggested diagnostic tests and emphasis on the adjunctive role of antimicrobial therapy, would be more useful to practicing physicians. In fact, the current guideline process has been heavily influenced and perhaps eroded by commercial marketing strategies. It is not surprising that a pharmaceutical company, on learning that their product has been included in a guideline, will use that guideline to promote that product. Indeed, considerable effort and expense are used to bring the virtues of specific products to the entire clinical community, including members of the guideline development team.[48] Unfortunately, this creates concern about the integrity of the guideline, no matter how independent the guideline developers consider themselves.

One successful approach to implementation (achieving compliance with guidelines) has come through the development of care paths, also known as clinical practice pathways. These reflect evidence-based recommendations for processes and provide specific and assessable quality measures, including timelines. As noted earlier, among the most successful have been those for community-acquired pneumonia. Benchmarks are given for intervals from time of emergency room arrival to various diagnostic and therapeutic milestones. Hospital performance is closely monitored and is reported to various regulatory agencies such as The Joint Commission (formerly The Joint Commission on Accreditation of Healthcare Organizations, JCAHO). In general, what is reported and measured is "what is done," not "what is not done." So there is little incentive to withhold antibiotics, and there is strong incentive to give them quickly.

Complicating the situation is the fact that physicians cannot currently provide evidence that a particular patient does not need an antibiotic. Conventional culture techniques require a couple of days before "no growth" can be confirmed, and there is always a small possibility of a false negative culture result. Molecular techniques such as gene amplification still require 4 to 6 hours to quantify pathogenic organism load. Although direct detection techniques are promising, and the availability of such good rapid diagnostics could play an important role in empowering physicians to deny antibiotics, they are currently costly and not suited to bedside use.

Surgeons and antibiotic use

Surgeons have taken important steps toward refining their use of prophylactic antibiotics. The Surgical Infection Prevention Project and its successor, the Surgical Care Improvement Project have established performance measures for timely and appropriately selected perioperative administration of antibiotics.[49] Audits suggest that the opportunity to improve performance in the predictable elective perioperative setting is substantial.[50,51] In the US, the government is encouraging surgical teams to optimize antibiotic administration through pay-for-performance incentives. Application of industrial process control techniques have the potential to substantially improve compliance, with guideline recommendations in highly monitored and readily reviewed settings such as the operating room.[52] Development, promulgation, and monitoring of adherence to guidelines in less visible settings where prompt empiric therapy is required (eg, intraabdominal sepsis) is no less important, but may prove far more challenging.

Changing the norms

General prescribing behaviors appear difficult to change in the short-term.[53] Even if the norms could be changed and prescribing behavior could be modified, the impact of lowering antibiotic use on resistance is far from certain. The fitness cost of maintaining resistance appears to be small in many cases. For example, stool samples obtained from children never exposed to legacy antibiotics such as streptomycin nevertheless contain organisms that are resistant to that drug (BR Levin, personal communication). In addition, concern will always persist within each specific patient-physician relationship that the shifting norms favoring lower prescribing might result in denial to this patient who actually needs antibiotics.

Given these constraints, the initial strategy to reduce antibiotic resistance should probably focus more on preventing transmission of resistant organisms. Tools include infection control, hygiene, and vaccination. There are several layers to this effect. Most simply, reduced transmission means that whatever resistant strains are present cause fewer infections. Also, preventing transmission may disproportionately affect resistant strains. Theoretical models of hospital infections suggest this may occur if resistant strains are more dependent on within-hospital transmission than are sensitive strains. Recent use of the pneumococcal conjugate vaccine, which targets particular serotypes, has reduced resistance (perhaps temporarily) because the targeted serotypes happen to be those with the highest percentage of resistance.[54] Finally, infection control efforts may deliberately target resistant organisms, as in the case of the highly successful "search and destroy" policy for methicillin-resistant *Staphylococcus aureus* in the Netherlands.[55] Unlike modifications of antibiotic use, these interventions rarely involve tradeoffs between the individual's well-being and the risk of resistance to others; in general, all patients benefit from reductions in transmission. Such aggressive measures raise awareness that resistance is a problem, and may serve to soften reluctance to limit prescribing. The main point for the surgical community is that strict adherence to transmission control including absolute fidelity to gloving, gowning, and other barrier precautions; rigorous hand hygiene, and perfect aseptic technique are essential to everyday practice to ensure long-lasting efficacy of antimicrobial drugs. Here, an expectation of 100% compliance with transmission control procedures can and should be established by surgical personnel.

Prescribing guidelines themselves can be modified to ensure that even if antibiotics are used, development of resistance is minimized. Drug combinations have been used widely in HIV and tuberculosis to minimize emergence of resistance and could also prove useful in the case of bacterial infections.[56] The fact that a single agent is "as effective" as combination therapy in controlling an infection by a susceptible organism offers no insight concerning the emergence of resistance. Antimicrobial cycling has been proposed as a strategy for controlling resistance, but mathematical models provide little support for the theoretic rationale behind such programs, and most clinical trials have shown no benefit. The simplest and most effective guideline change may direct shortening courses of antibiotic treatment. With rare exception, there is no evidence to support traditional 10-day or 2-week courses of antibiotics. Short-course therapy for acute otitis media, tonsillopharyngitis, and sinusitis is slowly gaining support.[57] The short-course paradigm is, in principle, widely extensible to the broad range of antibiotic prescriptions written by surgeons in both the hospital and ambulatory settings.

Measures aimed at controlling transmission and guideline revisions are important, but by themselves, will be insufficient to control the explosion of antibiotic resistance that affects much of the globe. Fundamental changes in patient expectations, in marketing and indications for antibiotic use, and in physician prescribing behavior must occur. Existing incentives must be revised and adjusted to ensure that all stakeholders are engaged and perceive good reason to control antibiotic use. Although education concerning the eventual loss of effectiveness of antibiotics is important, it has been and likely will continue to be generally ineffective at changing behaviors within the physician-patient dyad.[58] Patient and physician are dealing with an illness in the present and substantially discount problems that their behaviors might cause in the distant future. Policy options aimed at physicians might include changes in the way physicians are paid for prescribing antibiotics to include some performance metric for accuracy and limitation of antibiotic use. Patients might be motivated to seek fewer and shorter courses of antibiotics by delaying or at least staging the dispensation (initially dispensing a short course and requiring the patient to return if there is evidence of ongoing infection or a positive culture). Alternatively, patients might be reimbursed differently for antibiotic prescriptions.

In conclusion, antibiotic overuse is a complex, multifactorial problem and a challenge to our ability to continue using these drugs. Although economic incentives exert a powerful influence, other factors such as social norms that govern interactions between patients and physicians and between physicians are important in determining the level of antibiotic use. Social norms can be efficient pathways to solutions where the transaction costs of identifying optimal solutions in a particular situation are high. The present norm of empiric prescription of long antibiotic courses without obligation by either physician or patient to verify diagnosis or effectiveness seems unlikely to change unless incentives within the patient-physician dyad are restructured.

APPENDIX: THE McDONNELL NORMS GROUP

The McDonnell Norms Group, sponsored by the James S McDonnell Foundation, aims to identify core principles in the behavioral, cognitive, and social sciences that enable the responsible application of information for the public good. The group intends to close the gap between gathering, synthesis, and provision of information—activities that culminate in the development of reasonable recommendations—and the adoption of new behaviors that reflect those recommendations. The group includes scientists and policy experts with backgrounds ranging from clinical surgery to evolutionary biology.

The James S McDonnell Foundation is a not-for-profit foundation that uses its resources to catalyze development of new knowledge and insight at the intersection of specific disciplines, such as complex systems science and neurobiology.

Timothy G Buchman, Department of Surgery, Washington University in St Louis, St Louis, MO

Jonathan Dushoff, Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ

Mark B Effron, Eli Lilly and Co, Indianapolis, IN

Paul R Ehrlich, Department of Biologic Sciences, Stanford University, Stanford, CA

Susan Fitzpatrick, James S McDonnell Foundation, St Louis, MO

Ramanan Laxminarayan, Resources for the Future, Washington DC

Bruce Levin, Department of Biology, Emory University, Atlanta, GA

Simon A Levin, Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ

Marc Lipsitch, Department of Epidemiology, Harvard School of Public Health, Boston, MA

Anup Malani, The Law School, The University of Chicago, Chicago, IL

Carol Nemeroff, Department of Psychology, Arizona State University, Tempe, AZ

Sarah P Otto, Department of Zoology, University of British Columbia, Vancouver, BC

Vimla L Patel, Department of Biomedical Informatics, Arizona State University, Tempe, AZ

Joseph S Solomkin, Department of Surgery, University of Cincinnati, Cincinnati, OH

REFERENCES

1. Bartlett JG. *Clostridium difficile:* old and new observations. J Clin Gastroenterol 2007;41:S24–S29.

2. Rubin RJ, Harrington CA, Poon A, et al. The economic impact of *Staphylococcus aureus* infection in New York City hospitals. Emerg Infect Dis 1999;5:9–17.
3. Howard D, Rask K. The impact of resistance on antibiotic demand in patients with ear infections. In: Laxminarayan R, ed. Battling resistance to antibiotics and pesticides: an economic approach. Washington DC: RFF Press; 2002:119–133.
4. Frazee BW, Lynn J, Charlebois ED, et al. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. Ann Emerg Med 2005;45: 311–320.
5. Laxminarayan R, Malani A. Extending the cure: policy responses to the growing threat of antibiotic resistance. Washington DC: Resources for the Future; 2007.
6. Aminov RI, Mackie RI. Evolution and ecology of antibiotic resistance genes. FEMS Microbiol Lett 2007;271:147–161.
7. Singer RS, Ward MP, Maldonado G. Can landscape ecology untangle the complexity of antibiotic resistance? Nat Rev Microbiol 2006;4:943–952.
8. McDermott PF, Zhao S, Wagner DD, et al. The food safety perspective of antibiotic resistance. Anim Biotechnol 2002;13: 71–84.
9. Carter RJ, Sorenson G, Heffernan R, et al. Failure to control an outbreak of multidrug-resistant *Streptococcus pneumoniae* in a long-term-care facility: emergence and ongoing transmission of a fluoroquinolone-resistant strain. Infect Control Hosp Epidemiol 2005;26:248–255.
10. Wang YC, Lipsitch M. Upgrading antibiotic use within a class: tradeoff between resistance and treatment success. Proc Natl Acad Sci USA 2006;103:9655–9660.
11. Wang EE, Einarson TR, Kellner JD, Conly JM. Antibiotic prescribing for Canadian preschool children: evidence of overprescribing for viral respiratory infections. Clin Infect Dis 1999;29: 155–160.
12. Mean M, Pavese P, Vittoz JP, et al. Prospective assessment of fluoroquinolone use in a teaching hospital. Eur J Clin Microbiol Infect Dis 2006;25:757–763.
13. Palmer NO, Martin MV, Pealing R, et al. Antibiotic prescribing knowledge of National Health Service general dental practitioners in England and Scotland. J Antimicrob Chemother 2001;47:233–237.
14. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. J Antimicrob Chemother 2005;56:930–936.
15. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. J Antimicrob Chemother 2005; 56:569–574.
16. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991–1999. Ann Int Med 2005;38:525–533.
17. McCaig LF, Besser RE, Hughes JM. Antimicrobial drug prescription in ambulatory care settings, United States, 1992–2000 Emerg Infect Dis 2003;9:432–437.
18. Roumie CL, Halasa NB, Grijalva CG, et al. Trends in antibiotic prescribing for adults in the United States–1995 to 2002. J Gen Intern Med 2005;20:697–702.
19. Koonin EV, Makarova KS, Aravind L. Horizontal gene transfer in prokaryotes: quantification and classification. Ann Rev Microbiol 2001;55:709–742.
20. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005;365:579–587.
21. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851–1853.
22. McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis 1983;5:1033–1048.
23. Seppala H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med 1997; 337:441–446.
24. Enne VI, Livermore DM, Stephens P, Hall LM. Persistence of sulphonamide resistance in *Escherichia coli* in the UK despite national prescribing restriction. Lancet 2001;357:1325–1328.
25. Belongia EA, Sullivan BJ, Chyou PH, et al. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant *Streptococcus pneumoniae* carriage in children. Pediatrics 2001;108:575–583.
26. Foster KR, Grundmann H. Do we need to put society first? The potential for tragedy in antimicrobial resistance. PLoS Med 2006;3:e29.
27. Laxminarayan R. Battling resistance to antibiotics and pesticides: An economic approach. Washington, DC: RFF Press; 2003.
28. Albers AB, Siegel M, Cheng DM, et al. Relation between local restaurant smoking regulations and attitudes towards the prevalence and social acceptability of smoking: a study of youths and adults who eat out predominantly at restaurants in their town. Tob Control 2004;13:347–355.
29. Gilpin EA, Lee L, Pierce JP. Changes in population attitudes about where smoking should not be allowed: California versus the rest of the USA. Tob Control 2004;13:38–44.
30. Skeer M, Land ML, Cheng DM, Siegel MB. Smoking in Boston bars before and after a 100% smoke-free regulation: an assessment of early compliance. J Public Health Manag Pract 2004; 10:501–507.
31. Hart AM, Pepper GA, Gonzales R. Balancing acts: deciding for or against antibiotics in acute respiratory infections. J Fam Pract 2006;55:320–325.
32. Warneryd K. Transaction cost, institutions and evolution. J Econ Behav Org 1994;25:219–239.
33. Mangione-Smith R, McGlynn EA, Elliott MN, et al. Parent expectations for antibiotics, physician-parent communication, and satisfaction. Arch Pediatr Adolesc Med 2001;155:800–806.
34. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. Br J Gen Pract 2003;53:871–877.
35. Fischer T, Singer AJ, Lee C, Thode HC Jr. National trends in emergency department antibiotic prescribing for children with acute otitis media, 1996-2005. Acad Emerg Med 2007;14: 1172–1175.
36. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med 2006;355:666–674.
37. Finkelstein R, Rabino G, Mashiah T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. J Thorac Cardiovasc Surg 2002;123:326–332.
38. McNicholas S, Barber A, Corbett-Feeney G, Cormican M. Linezolid audit: similarities and contrasts with published experience. J Antimicrob Chemother 2006;57:1008–1009.

39. Graham JP, Boland JJ, Silbergeld E. Growth promoting antibiotics in food animal production: an economic analysis. Public Health Rep 2007;122:79–87.
40. Harder B. McDonald's cutback in antibiotics use could reduce drug-resistant bacteria. Available at: http://sciencenewsmagazine.org/articles/20030628/food.asp. Accessed October 15, 2007.
41. Rubinstein E. Short antibiotic treatment courses or how short is short? Int J Antimicrob Agents 2007;30:S76–9.
42. Marra F, Monnet DL, Patrick DM, et al. A comparison of antibiotic use in children between Canada and Denmark. Ann Pharmacother 2007;41:659–666.
43. Malmvall BE, Mölstad S, Darelid J, et al. Reduction of antibiotics sales and sustained low incidence of bacterial resistance: Report on a broad approach during 10 years to implement evidence-based indications for antibiotic prescribing in Jönköping County, Sweden. Qual Manag Health Care 2007;16:60–67.
44. Bosk CL. Forgive and remember: managing medical failure. 2nd ed. Chicago: University of Chicago Press; 2003.
45. Pratter MR. Cough and the common cold: ACCP evidence-based clinical practice guidelines. Chest 2006;129:72S–74S.
46. D'Innocenzio A. Quality a concern at retail health clinics. Available at: http://www.msnbc.msn.com/id/20215467/. Accessed October 17, 2007.
47. McDonnell Norms Group. Enhancing the use of clinical guidelines: a social norms perspective. J Am Coll Surg 2006;202:826–836.
48. Wall LL, Brown D. The high cost of free lunch. Obstet Gynecol 2007;110:169–173.
49. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis 2006;43:322–330.
50. Rioux C, Blanchon T, Golliot F, et al. [Audit of preoperative antibiotic prophylaxis in a surgical site infections surveillance network.] Ann Fr Anesth Reanim 2002;21:627–633.
51. Gul YA, Lian LH, Jabar FM, Moissinac K. Antibiotic prophylaxis in elective colorectal surgery. ANZ J Surg 2002;72:275–278.
52. Parker BM, Henderson JM, Vitagliano S, et al. Six sigma methodology can be used to improve adherence for antibiotic prophylaxis in patients undergoing noncardiac surgery. Anesth Analg 2007;104:140–146.
53. McDonnell Social Norms Group. Battling bad behavior. The Scientist 2006;20:51.
54. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737–1746.
55. Vos MC, Ott A, Verbrugh HA, et al. Successful search-and-destroy policy for methicillin-resistant *Staphylococcus aureus* in The Netherlands. J Clin Microbiol 2005;43:2034–2035.
56. Patel SM, Saravolatz LD. Monotherapy versus combination therapy. Med Clin North Am 2006;90:1183–1195.
57. Pichichero ME. Short course antibiotic therapy for respiratory infections: a review of the evidence. Pediatr Infect Dis J 2000;19:929–937.
58. McNulty CAM, Boyle P, Nichols T, et al. Don't wear me out—the public's knowledge and attitudes to antibiotic use. J Antimicrobial Chemotherapy 2007;59:727–738.