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Prospects & Overviews

Accounting for variation in and overuse of antibiotics among humans

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Abstract

Worldwide, antibiotic use is increasing, but many infections against which antibiotics are applied are not even caused by bacteria. Over-the-counter and internet sales preclude physician oversight. Regional differences, between and within countries highlight many potential factors influencing antibiotic use. Taking a systems perspective that considers pharmaceutical commodity chains, we examine antibiotic overuse from the vantage point of both sides of the therapeutic relationship. We examine patterns and expectations of practitioners and patients, institutional policies and pressures, the business strategies of pharmaceutical companies and distributors, and cultural drivers of variation. Solutions to improve antibiotic stewardship include practitioners taking greater responsibility for their antibiotic prescribing, increasing the role of caregivers as diagnosticians rather than medicine providers, improving their communication to patients about antibiotic treatment consequences, lessening the economic influences on prescribing, and identifying antibiotic alternatives.

INTRODUCTION

The global consumption of antibiotics is rapidly increasing as is concern about antibiotic resistance [1–4] as a collective ecological condition of late industrialism [5–7] and as a modern day tragedy of the commons.[7–9] As such, antibiotic use demands stewardship on both a local and global scale.[10,11] Despite their undisputed benefits in patients with clear-cut and life-threatening bacterial infections, it is widely acknowledged that antibiotics are both grossly misused and overused [2,3,12] leading to drug resistance, and to pernicious effects on the microbiome that place users at greater risk for a growing list of health conditions.[13–16] Unnecessary antibiotic treatment also constitutes an economic burden to both health care systems and to families when medications are paid out of pocket. This burden increases when antibiotic resistant infections emerge given that they take longer to treat, are more costly, and often associated with worse outcomes.

In this paper, we provide a brief overview of antibiotic use in both developed and low and middle-income countries (LMIC), highlighting regional differences. Our focus is on what drives antibiotic overuse. We consider the prescription practices of different types of health care practitioners and medicine dispensers as well as the self-treatment practices of community members. Taking a systems perspective that considers pharmaceutical commodity chains, we examine antibiotic overuse from the vantage point of both sides of the therapeutic relationship, institutional policies and pressures, and the business strategies of pharmaceutical companies and distributors. Our major concern is on antibiotics imbibed among out-patients, since it represents the majority of all usage, and because in-hospital antibiotic use involves greater complexity in sicker patients. Our review draws upon studies of human antibiotic use conducted by researchers from several disciplines. Based on our review, we offer suggestions on how to improve antibiotic stewardship.

ANTIBIOTIC CONSUMPTION AND VARIATION IN OVERALL USE

Global trends in antibiotic use

Direct antibiotic use for humans in 2011 was estimated at 70 billion doses, or approximately ten antibiotic doses annually for every man, woman, and child on earth.[12] At a global level, antibiotic consumption has been steadily increasing; between 2000 and 2015, antibiotic consumption increased 39% globally, reflecting a 77% increase among LMICs, more than offsetting a 4% decrease among high-income countries (HICs).[2] Antibiotic usage rates are highest for young children.[17–24] Young children, at critical developmental stages, are commonly exposed to antibiotics in low-income settings. As reported from a large longitudinal household-based study, children from eight LMIC countries consumed an average of 4.9 antibiotics courses annually during the first two years of life.[25]

Children usually suffer from 4 to 6 upper respiratory tract infections (URIs) annually compared to two to three episodes in adults. Most URIs are self -limited and at least 80% are not caused by bacteria.[26] However, URIs are the most common ailments treated by antibiotics,[27] especially in young children. In China, 78% of outpatient children with the common cold received an antibiotic prescription,[28] and in Turkey, 100% of children presenting to an emergency room with an influenza-like illness were prescribed an antibiotic.[29] Notably, even in the USA, where antibiotic prescriptions for children have dropped substantially over the last two decades, unnecessary prescriptions of antibiotics remain high,[30] and there is significant variation by practitioner.[31]

Data consistently show high prescription rates. In a large study in China, the antibiotic prescription rates in acute upper respiratory infections, diarrhea in children <5 years, and fever or cough symptoms all exceeded 55%.[32] In the eight-LMIC country study,[25] antibiotics were used in about 40% of all episodes of either upper respiratory illness or (non-bloody) diarrhea. In a prospective observational cohort study in South India, more than half the children had been treated with antibiotics for respiratory infections or diarrhea; most (89.2%) had received antibiotics by the age of 6 months. Although there is little consideration of the biological costs of antibiotic use, there is great concern that the health benefits of widespread antibiotic availability for poor children will be missed if use is restricted.[33]

Emerging trends include internet sales; studies in the USA, UK, and China have found numerous online pharmacies selling antibiotics without a prescription or after providing a cursory pre-sale consultation.[34–37] Another source of questionable antibiotic sales are primary consultations over the telephone; in an analysis of recent calls with complaints of an acute respiratory infection to a direct-to-consumer telemedicine service in the USA, 86% of the telephone prescriptions were for a broad-spectrum agent compared to 56% for physician offices.[38] However, high-quality longitudinal data in the United States also has documented significant shifts in antibiotic use. Outpatient antibiotic consumption, as measured by expenditure, decreased 16.6% from 2010 to 2015.[39] Similarly, the proportion of people who reported using an antibiotic in the prior 30 days declined from 1999–2002 (6.1%) to 2011–2012 (4.1%).[40]

The distribution of the classes of antibiotics consumed also is changing. In 2000, broad-spectrum penicillins were the most widely prescribed antibiotics in the world; the growth in usage by 2010 was mostly driven by increases in broad-spectrum penicillin, cephalosporins, macrolides, and fluoroquinolones.[12] However, global trends reflect a composite of regional differences; for example, cephalosporin consumption rose in LMICs but declined in HICs, as did consumption of other broad-spectrum agents such as macrolides, fluoroquinolines, and oxazolidiones (Figure 1).[2] Thus, global trends often hide local practices.

Differences in prescription patterns by region

In the USA, there is substantial geographic variation in out-patient antibiotic consumption (Figure 2, panel B).[20] Consumption rates are highest in the South and lowest in the West, with the Northeast and Midwest being intermediate in consumption; these trends have been consistent over time, and are essentially the same for all age groups.[19] Similarly, antibiotic prescriptions given in physicians' offices in 2012–2013 for respiratory conditions were lowest in the Pacific region and highest in the East South-Central region, a trend also observed for the rates at which respiratory illnesses were diagnosed.[41] Such variation also was seen in commercial health plans, with those in the South Central census division showing the highest use of three antibiotic-related measures.[42] In total, the national-level data indicate consistent geographic variation that is stable across multiple years and patient ages. The differences are not small; per capita antibiotic use in the South is more than 50% higher than in the West, across tens of millions of people,[20,21] and are consistent across different data bases.[43]

Similar to the US, overall antibiotic consumption decreased significantly in Europe from 1997 to 2009.[44,45] Nevertheless, there is extensive variability in usage between countries; with two-fold differences in per capita consumption between countries bordering the Mediterranean (Greece, Cyprus, Italy and France), and northern European countries (Netherlands, Sweden, Norway, Germany)[44] [Figure 3].

Several cross-country comparisons are also worth considering.[2,12] For example, data from Sweden documents annual per capita antibiotic consumption that is only 40% of that in the USA; a pattern that holds true across every age group.[21,46] Further, Swedish outpatient usage of macrolides and cephalosporins (at 3% each of the total), contrasts with 23% and 14%, respectively, for the USA.[39] As in the USA, antibiotic use fluctuates with season, the highest use being in the winter months (Figure 4). In general, the countries that have the highest rate of total use also had the largest seasonal differences in antibiotic use.

In contrast to the USA and most of Europe, a high proportion of antibiotics sold in LMIC countries is without prescriptions at local pharmacies.[47] These shops are often staffed by untrained attendants who commonly dispense only a few antibiotic pills at a time at a customer's request. A metanalysis of 38 studies from 24 countries where

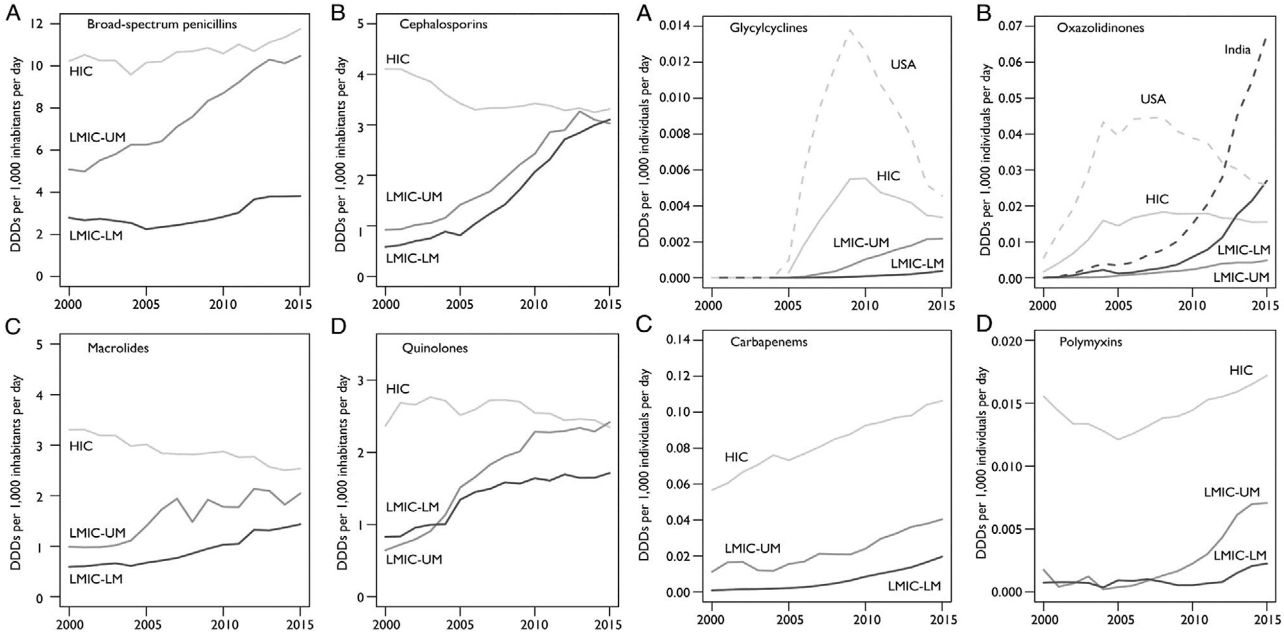

FIGURE 1 Changes in global consumption of eight different classes of antibiotics between 2000 and 2015, stratified by level of country income: high-income (HIC), low- and upper-middle-income (LMIC-UM), low- & lower-middle-income (LMIC-LM) [reprinted from Klein 2018][2]

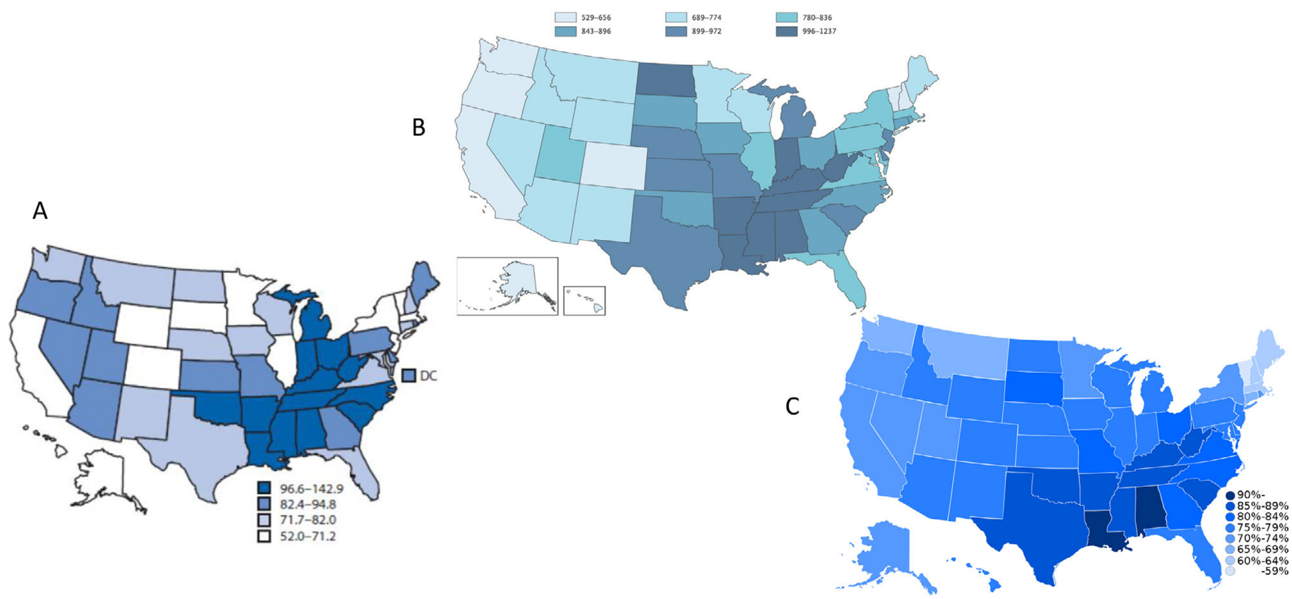

FIGURE 2 Comparison of opiate prescribing, antibiotic prescribing, and rates of church attendance, by state, in the USA. Panels: (A) Opiate prescribing rates are per 1000 population in 2012 (reprinted from Paulozzi 2014[178]). (B) Antibiotic prescribing rates per 1000 population (reprinted from Hicks et al. 2013 [20]); the same trends held in 2011, and as well when the population was stratified by age (children <2 years, age 2–64 years, elderly (>65) [reprinted from Hicks Clin Infect Dis 2015][19]; (C) Church attendance rates are per 100 adults in 2014 [reprinted from Pew, 2014][148]

antibiotics are technically available by "prescription only" found that the overall proportion of non-prescription supplied antibiotics was 62%, due both to patient request and pharmacy staff recommendation. Antibiotic dispensing by pharmacy staff often mirrors practitioner prescribing, since they are aware of the actual prescriptions. These patterns are then reproduced by untrained local medical practitioners who purchase medicines from the same local pharmacies using them as a source of information as well as supply.[48,49] The scale of this issue is substantial in countries such as India where these "doctors" see up to 75% of primary care consultations in rural areas.[50–55] Although sales of several antibiotics classes without prescription are technically illegal in many LMIC, enforcement is difficult in rural areas with few doctors

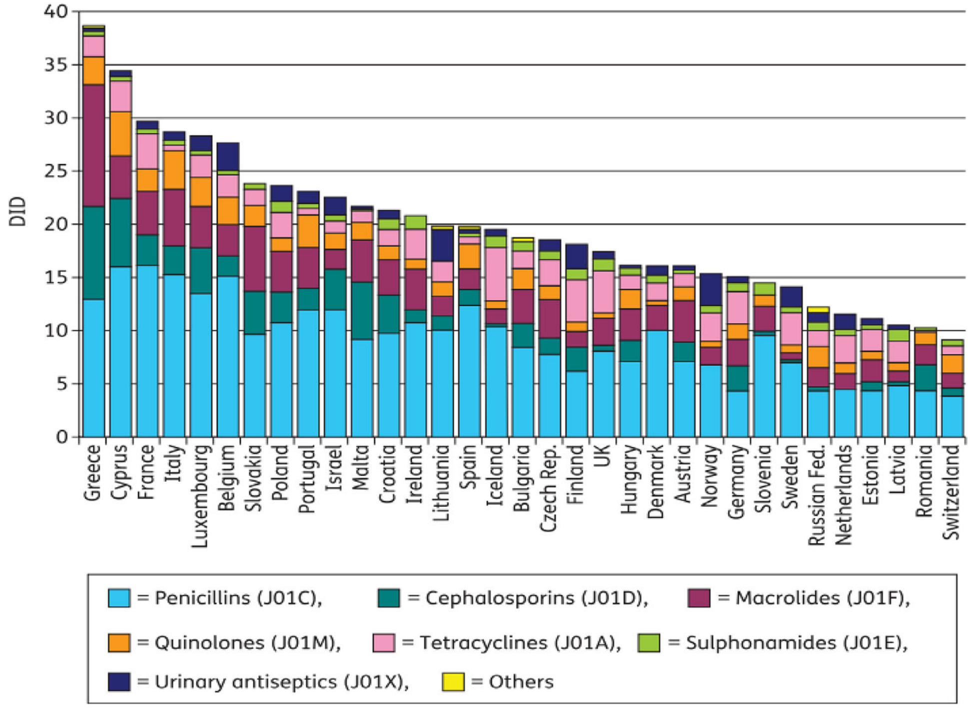

FIGURE 3 Antibiotic consumption in Europe in 2009 by antibiotic class [reprinted from Adriaenssens, 2011][44]

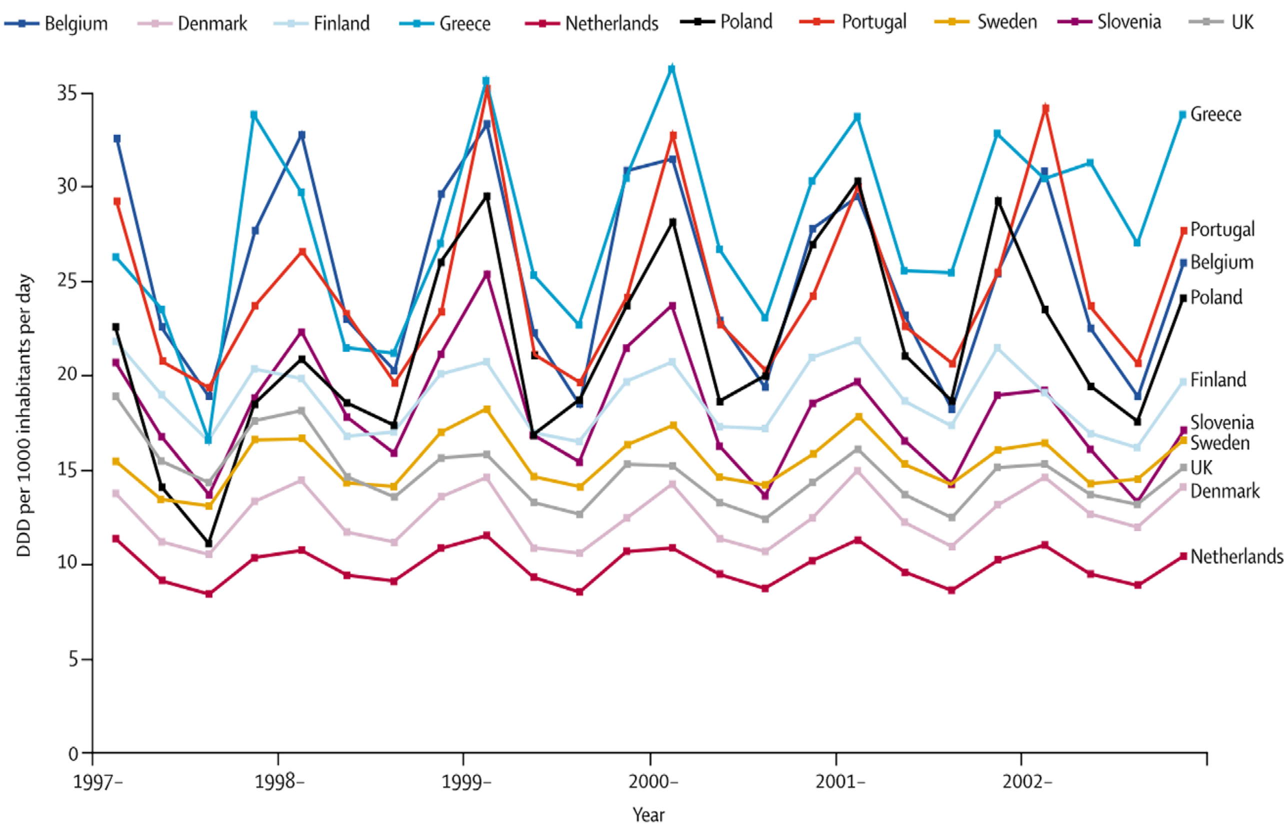

FIGURE 4 Seasonal fluctuations in antibiotic use in 10 European countries, 1997 to 2002, highlighting winter peaks [reprinted from Goossens 2005][45]

and in urban settings where the poor consult pharmacy staff for common ailments.

FACTORS DRIVING VARIATION IN ANTIBIOTIC USE AND OVERUSE

Studies have identified a wide range of practitioner, patient, health system, and pharmaceutical industry-related factors contributing to differences in rates of antibiotic misuse and overuse. Quantitative studies largely provide correlational data while qualitative studies provide more contextual and processual accounts of how multiple factors act in concert and reflect broader cultural considerations. We briefly highlight well-documented drivers of antibiotic overuse and identify other potential factors influencing the pharmaceutical practice of both trained practitioners working in different clinical practices, and untrained local "doctors" and dispensing pharmacy staff.

Variation according to characteristics of practitioners

A critical aspect of prescription practices is provider-level variation. In a large national study of acute respiratory infections among US veterans, the 10% of providers who prescribed the most antibiotics provided an antibiotic in at least 95% of their visits versus <40% for the lowest-rate prescribers.[56] In a study examining 29 pediatric group practices affiliated with an outstanding teaching hospital in the USA, the variation in per capita antibiotic prescribing between the practice that prescribed the least and the one prescribing the most exceeded 100%, and for broad-spectrum antibiotics, 400%.[31]

The age of practitioners has been correlated with the likelihood of an antibiotic prescription. A USA-based study of pediatric outpatient visits for common upper respiratory conditions that do not require antibiotics found that older providers were four times more likely to prescribe an antimicrobial than providers ≤30 years old (IRR, 4.21; 95% CI, 2.96–5.97).[57] Similarly, in a study of more than 10,000 family physicians in Ontario who collectively prescribed 5.6 million antibiotic courses, the number of physician years in practice was an important determinant of the duration of antibiotic courses. Prescriptions of longer duration (>8 days) were disproportionately prescribed by late-career physicians (in practice >25 years) (38.6% of their total antibiotic prescriptions) compared to mid-career (11–25 years) (34.4%), or early career (<10 years) physicians (30.5%).[58] Taken together, these findings are consistent with the hypothesis that older physicians have greater reliance on antibiotics than their younger colleagues, pointing to opportunities for educational interventions.

Antibiotic choices also vary by practitioner type. Azithromycin is the most commonly prescribed antibiotic in the United States, although it is infrequently recommended for pediatric conditions.[59,60] However, in a national study of oral antibiotic use, amoxicillin and azithromycin were the two most commonly prescribed agents in children. Most antibiotics for children were prescribed by pediatricians (39%) and family practitioners (15%), but family practitioners were significantly more likely to prescribe azithromycin than pediatricians, across all ages in childhood.[59,61,62]

Nurse practitioners (NPs) and physician assistants (PAs) in the USA prescribe antibiotics more frequently compared with physician-only visits, including visits overall (17% vs. 12%, $P < 0.0001$) and for acute respiratory infections (61% vs. 54%, $P < 0.001$).[63] While the antibiotic prescribing rate among physicians in the US decreased from 2005 to 2010, it increased for PAs and NPs,[63] providing another target group for educational efforts. Free-standing out-patient clinics ("doc-in the-box") have been a rapidly increasing venue for patient care; often staffed with PAs and NPs, antibiotic prescribing is at high rates.[63]

Variation according to public understanding of the need for antibiotics

Studies from around the globe have documented that the public is poorly informed about which common health problems are cured by antibiotics, whether antibiotics are effective against all types of "germs," and which illnesses are of viral or bacterial origin.[55–57] For example, most Australian parents believed that antibiotics are needed for children's common respiratory infections: for acute otitis media (92%), sore throat (70%), and cough (55%).[64] In Italy, 41% of parents believed that bacteria are a cause of the common cold, treatable by antibiotics.[65] In a Polish study,[66] 80% of respondents recognized that antibiotics "kill" bacteria, but many believed that antibiotics also kill viruses (60%), and are effective against flu (49%), and colds (36%). Across Europe, 57% of those surveyed were unaware that antibiotics were ineffective against viruses, and 44% did not know that antibiotics have no effect against colds or influenza.[67,68] In a North Carolina study, 53% of respondents incorrectly believed that antibiotics are effective for treating flu or the common cold, which did not differ significantly by sex, family status, or education level.[69] In an inner–city emergency department in the USA, 75% and 42% of patients believed that antibiotics were effective against bacterial and viral illnesses, respectively. Many lumped all types of pathogens together adopting a "germs are germs" attitude.[70] And among those who differentiated the two types of infection, many still accepted a "why take a risk" or "can't hurt" position about taking antibiotics, reflecting attitudes of many practitioners.

Another observation pertains to how patients respond to doctors when told their illness is caused by a virus and that they are not in need of antibiotics. Some patients interpret a virus diagnosis as a "just a virus" message, which trivializes their illness.[71] Recognizing this, some doctors are inclined to prescribe an antibiotic to maintain good social relations with the patient; the symbolic act of prescribing a medicine eclipses treatment guidelines.[72]

In LMIC, antibiotics are often seen as "strong," magical medicines, capable of both curing and preventing a range of illness.[73] However, there is considerable confusion among the public about which drugs are antibiotics.[74,75] The Philippines has one of the highest levels of antibiotic self-medication in Southeast Asia, consistent with easy access in both urban and rural areas at local provision (*sari sari*) shops and pharmacies. Study participants (>80%) often believe that antibiotics are effective against cough or cold.[76]

Antibiotics are commonly used to self-treat health problems for which they were never intended (off-label use). Examples include: (i), in China, the actions of antibiotics and nonsteroidal anti-inflammatory drugs are often conflated, as *Xiaoyanyao*, drugs that can eliminate inflammation,[77–80] leading to antibiotic use for conditions with self-limited inflammation; (ii), in Nigeria, women are increasingly using antibiotics to reduce menstrual problems (cramps, heavy flow, headaches, pimples/acne, moodiness, tender breasts, backache, joint and muscle pain) and to prevent "infections" from feminine sanitary products [81,82]; (iii), in Thailand, tetracycline is commonly used for women's "uterus" complaints, termed *moot luuk*, manifesting as vaginal discharge and pelvic pain [83,84]; and (iv), a common (world-wide) practice is self-treatment of wounds with crushed antibiotic capsules to dry them, reduce pain, and treat infection.[76,85–89]

A common behavior adopted in many countries is taking antibiotics to enable one go to work or school when ill,[90] or to delay illness onset when feeling off until the weekend, or to prevent a "bug going around." Among Chinese university students, 29.6% had self-medicated with antibiotics in the prior year, 23% had used antibiotics for prophylaxis against illness [91]; and a majority (63%) kept a personal antibiotic stock at home. Some workers, at the economic margin, take antibiotics to prevent latent illness from flaring up given that their survival depends on being able to work.[92] For example, in the USA, left-over antibiotics are taken by those employed in jobs that have fixed sick-leave provisions and high job insecurity to manage respiratory symptoms from getting worse, prevent others from catching their illness, or to prevent illness when coworkers are ill.[93]

Another pattern of antibiotic prophylaxis is harm reduction. In the Philippines and Thailand, antibiotics are commonly used by both commercial sex workers and their clients for protection before or after risky practices.[94–96] In China, commercial sex workers routinely take antibiotic injections for harm reduction.[97] In India, young men fearing they may be developing an STI after unprotected sex self-treat with an antibiotic purchased at a pharmacy when they feel vague bodily sensations.[98]

Patient expectations and the pressure to prescribe

One of the most important factors linked to overprescribing antibiotics is patient expectations.[99,100] Physicians' perceptions of what patients expect during a consultation have been strongly associated with antibiotic prescribing[65,101–105] and often described in the literature by the rubric "patient pressure." Doctors' perceptions of patient expectations may be accurate or far exceed patient requests and demands.[99,106–108] However, practitioners who have sufficient time to educate and reassure patients, especially when they have an established relationship, often are able to reassure patients antibiotics are not needed.[109–111] For example, in a German study of patients with upper respiratory tract infections,[112] 71% of those expecting an antibiotic prescription reported that they would trust their physician if an explanation were provided for why a prescription was unnecessary, and a further 7% reported that although unsatisfied, they would accept the decision; nevertheless, >20% would remain unsatisfied.

Patient "pressure" is often indirect and strategic. Patients may not demand antibiotics outright, but rather infer their need through the way they present the severity and prolonged nature of an illness, state that antibiotics worked in the past for a similar problem, or by reference to life circumstance, such as an upcoming trip, or a work-related event [113–115]; this is particularly an issue with minor infections involving the respiratory tract, which are among the most common reasons that patients seek medical attention.[112] In the USA, practitioners are commonly faced with a mother's appeal for an antibiotic enabling her to return to work lest she lose her job, or to treat a sick child's illness enabling them to return to school or day care. When practitioners receive indirect pressure to prescribe, they often comply to maintain good social relations with the patient and to reassure them that their complaint is being taken seriously.[116]

While practitioners vary in their response to perceived patient demands, many prescribe against their own assessment of patient need. In a systematic review, perception that the patient had a desire to receive antibiotics was one of only two factors strongly associated with prescribing (the other being a diagnosis of bronchitis).[103] These findings suggest that only educating physicians about medical best practices and the population-based consequences of antibiotic overuse will not be sufficient to curtail use in their everyday practices; educating the public is crucial.

Notably, in a systematic review, physician attitudes about their patients' expectations were found to affect their prescribing practice more than socio-demographic and personal factors [104]; complacency, defined as fulfilling what the physician perceived as the expectation, strongly drove prescribing, and fear of complications in the patient played a smaller role.[117] In a study involving 305 UK family physicians, doctors were presented with hypothetical patients; the increasing expectation from a patient that they would receive an antibiotic increased the physicians' willingness to prescribe, although prescribing antibiotics did not indicate that they thought the infection was of bacterial origin.[118]

Physicians caring for children are more likely to diagnose a bacterial illness and are much more likely to prescribe antibiotics if they believe that parents expect antibiotics. This is not a rare event, since in a US study, 43% of parents of a child with cold symptoms believed that antibiotics were necessary.[119] Such a belief was more frequent among Latino and Asian parents than in Caucasians. In the US, ethnicity and language variation are associated with differences in basic knowledge about antibiotics. In a Colorado survey, for example, non-Hispanic Whites had greater knowledge of appropriate antibiotic use, and English-speaking Hispanics had better knowledge than Spanish-speaking Hispanics.[120] However, there does not appear to be substantial ethnic variation in the US in the frequency of non-prescription antibiotic use,[121] and a systematic review of antibiotic-prescribing determinants that assessed ethnicity found no associations in most studies.[103] Nevertheless, ascertainment of availability from non-traditional providers (e.g., bodegas) is incomplete.

Variation due to specific social and economic interactions of prescribers and patients

Of the four most common factors reported to influence antibiotic over-prescription, three include practitioner time pressure, practitioner fatigue, and perceived patient expectation.[108,122–125] In a survey of 187 physicians working in retail clinics and primary care practices, inappropriate antibiotic prescribing was associated with feeling rushed; physician knowledge of guidelines did not predict patterns of prescribing.[126] Decision fatigue also contributes to antibiotic prescribing. Physicians may see antibiotic prescriptions as being an "easy" solution to maximize patient satisfaction; when tired, physicians are more likely to make the easy decision. Support for this concept comes from a study of 23 primary care practices in the USA showing that the proportion of patients receiving an antibiotic increased toward the end of physicians' shifts.[127]

Consistent with this observation are the results from a large-scale review of antibiotic prescribing in ambulatory patients with clinically obvious respiratory infections.[103] The investigators divided motivating factors into those operating at the patient or the physician level (Table 1). Patient factors, including specific findings related to pathology, appear appropriate. However, physician perception of a patient's desire to receive antibiotics was positively associated with prescribing in all six studies in which it was considered.[103]

The duration of symptoms influences prescription practice. Practitioners who do not have a well-established relationship with a patient fear that not prescribing what is expected will undermine patient confidence in them especially if an illness lasts longer than anticipated.[128] Nurse practitioner (NP)s and others with physician-extending practices are particularly vulnerable. They may suspect that patients will seek a more qualified practitioner to get the treatment they believe they need,[129,130] and will view the NP as not fully competent. In this scenario, antibiotic-prescribing represents a demonstration of their professional "power."

Notably, a factor that reinforces the tendency of GPs to meet patient expectation for antibiotics is the perception that antibiotic overuse is not a serious medical issue in their practice. An Australian study examined doctors' perceptions of the impact of antibiotic overprescribing for upper respiratory tract infections in a primary care practice like their own. Most GP respondents reported that they would prescribe antibiotics for a URI to meet patient expectations, and believed that antibiotic prescribing in primary care was not responsible for the development of antibiotic resistance [131]; antibiotic resistance was believed to be largely due to hospital prescribing, veterinary use of antibiotics, and antibiotic use in agriculture.

Financial incentives to prescribe and dispense antibiotics

Financial factors are major interacting drivers behind variation in antibiotic use. Financial incentives, profiteering from insurance schemes, and diverse forms of marketing [132] influence antibiotic prescribing. Practitioners who have a financial incentive to dispense medications prescribe more drugs. This holds true for antibiotics from Zimbabwe and Korea to Switzerland.[133–136] Several examples illustrate how this occurs.

In China, the financial incentives for prescribing antibiotics date from the barefoot doctor program. Introduced in 1968, the program is typically depicted as a strategy for good health at low cost through provision of integrated (traditional medicine and allopathic medicine) primary care. Less-recognized is that the program is largely responsible for popularizing the liberal use of antibiotics in the countryside. Barefoot doctors were permitted to profit from dispensing antibiotics and this became a primary source of their income.[137] When the barefoot doctor program was phased out in the mid-1980s, medical practitioners continued to prescribe antibiotics to obtain fees for services, and dispensing chemists began selling antibiotics without a prescription to meet popular demand. A country-wide survey in China between 2007 and 2009 [138] documented substantial antibiotic overprescribing despite shifts in best practice policy advocated by the government. The Chinese health sector is dominated by profit-driven hospitals operating in a "free" market in which services are largely paid out-of-pocket by patients.[139] Compensation for both hospitals and doctors is closely tied to pharmaceutical sales (Ding et al. 2019). As such, doctors [140] and pharmacies in China earn their livelihood from patients who have a strong preference for antibiotics and respond to this demand for antibiotics as means of increasing income.[141]

Although China has recently made great strides in prescription policy, implementation lags. In a national sample, non-prescription sales of antibiotics for pediatric diarrhea and URTIs were 48.5% and 70.1%, respectively.[142] Moreover, because self-treatment with antibiotics is so common,[142,143] doctors tend to prescribe more powerful agents and new antibiotic combinations unknown to the public, to differentiate their services from self-treatment. A similar phenomenon is common in India.[144,145] Through a network of pharmaceutical representatives (salespersons), the large pharmaceutical companies have introduced a steady stream of new branded drugs to doctors eager to have an edge in competitive health care markets.[146,147] Aggressive direct-marketing and a gift culture contribute to both over-prescription and use of proprietary drugs rather than cheaper generics.[148,149]

Financial gain from the overuse and misuse of antibiotics is multimodal, and associated with both lax implementation of laws and with outright corruption. In Europe, variation in antibiotic consumption is correlated with measures of corruption in both the health sector, and in society at large.[150] Uncertainty avoidance, the extent to which a society tolerates uncertainty and ambiguity, is a major driver of antibiotic utilization[151] that also correlates with societal levels of corruption and bribery.

Across Europe, total antibiotic consumption has been lower in countries that restrict direct pharmaceutical marketing to physicians, and is also lower in health systems where patients are generally required to visit the same family practitioner.[127,128,131] Such findings suggest that greater freedom to select a physician may exert increased pressure on physicians to try to please patients in situations in which the

TABLE 1 Systematic review of studies identifying factors associated with antibiotic prescribing for respiratory tract infections (Mackey & Nayyar, 2016)

Factor	No. of studies with: Positive association	Negative association	No significant association	Total no. of studies
Patient level				
Age	6		13	19
Male sex	1		9	10
Comorbidity	2		7	9
Medical insurance type	1		7	8
Ethnicity	1		6	7
Black versus white race		1	5	6
Fever	5		1	6
Bronchitis	5			5
Purulent sputum	5			5
Respiratory findings on physical exam	5			5
Desire for antibiotics	3		1	4
Smoker	3		1	4
Cough	1		2	3
Duration of illness	1		2	3
Household income		1	2	3
Pharyngitis	3			3
Rhinorrhea		2	1	3
Sinus pain on exam	3			3
Tonsillar exudate	3			3
Tympanic membrane abnormality	3			3
Physician level				
Specialty	6		2	8
Perception of desire for antibiotics	6			6
Severity of patient illness	4			4
High-volume practice	1		2	3
International medical graduate	2	1		3
Area-level				
Geographic location	1		6	7
Rural versus urban	3		4	7
Year of visit			4	4
Visit location (office, emergency department, hospital clinic)	1		2	3

specific indications for treatment are not rigid, which in reality includes most clinical scenarios. Antibiotic consumption also is greater in health systems in which more types of antibiotics are available.[152] A systematic review of qualitative studies assessing prescribing practice found that the effect of pharmaceutical marketing on physicians' decisions was mixed. However, studies that examined financial incentives found a positive association with prescribing.[104,153] The fact that pharmaceutical companies have extensive marketing practices indicates *per se* that they believe that such campaigns are effective for shaping physician attitudes, and ultimately their own sales.[154]

Cultural drivers of variation

"Culture" influences local perceptions of risk and illness, healthcare seeking behavior, and trust in and expectations from healthcare providers, including prescription practices.[155] The substantial intra- and international differences in antibiotic prescriptions in Europe and the United States cannot be fully explained by variation in health service provision.[152,156–161] One productive approach to studying variation is to quantify the effect of value-oriented dimensions of cultural differences (Table 2).[47,151,162] A few examples may be cited.

TABLE 2 Dimensions of culture used in comparative studies of medical practices (Hofstede, 2011)

Power distance	The extent to which citizens tolerate social inequality, and the way in which the power differential effects doctor:patient communication.
Uncertainty avoidance	The extent to which a society tolerates or responds to uncertainty and ambiguity; that is, the comfort level of citizens faced with uncertainty and the pressure for action to gain a sense of control.
Individualism versus collectivism	The extent to which individuality eclipses collectivist social values.
Masculinity	The extent to which masculine values associated with assertiveness, competitiveness, and stamina prevail and arechurch attendance by socially accepted.
Long-term versus short-term orientation	The extent to which pragmatic virtues guide future-oriented behavior inclusive of saving, persistence, and adapting to novel circumstances.
Indulgence	Extent to which a society condones and has policies that enable gratification of basic and natural human drives and the pursuit of personal enjoyment.

The culture of Switzerland is strongly influenced by and reflective of the surrounding countries of France, Italy, and Germany. Among Swiss hospitals, those in Italian-speaking areas consume the most antibiotics, followed by those in French-speaking and then German-speaking areas, trends that parallel the relative usage in the three adjacent countries.[163] Similar relationships have also been observed for outpatient prescribing.[164] These differences within one country with a relatively uniform medical payment and education system points to the importance of cultural factors as determinants of antibiotic usage.

The 2009 Eurobarometer study, conducted in 27 EU countries using cultural dimensions (Table 2), found that nearly half of the geographical variation in inappropriate antibiotic use could be explained by two dimensions: uncertainty avoidance and masculinity.[165–167] Compared with most Northern European countries, those in the Mediterranean, which also have the highest per capita antibiotic use in Europe, had far higher uncertainty avoidance scores. Increased antibiotic use has been associated with intolerance of ambiguity and uncertainty.[165] Low uncertainty tolerance may lead patients to respond poorly to messages that an illness (e.g., acute respiratory episode) is self-limiting, requiring only symptomatic therapy. Doctors also are more likely to be uncomfortable and prescribe an antibiotic when faced with symptoms most likely to due to a viral infection, but that overlap with bacterial infections. High uncertainty avoidance scores may also help explain intraregional differences in antibiotic use between Flemish Belgians and adjacent Dutch residents.[165] The former has among the highest uncertainty avoidance scores in Europe, whereas the Dutch have one of the lowest.[168]

Countries with high masculinity scores also tend to have a strong work ethos in which staying on the job is both respected and expected, except for serious illness. In such environments, antibiotics may be used more liberally since they are seen as a means of achieving functional health and returning to work rapidly.[165] This relationship may help explain the high level of ambulatory antibiotic consumption in the UK and the US, since both countries score low on uncertainty avoidance, but high on masculine work ethic values.

Cultural and social economic factors are closely tied to prescription patterns at multiple levels.[155] In Germany, where antibiotic use is much less than in France, patients are less likely to ask for antibiotics for cough or sore throat, and physicians are more likely to advocate waiting and ordering extra diagnostic tests.[159] Another important reason for these differences is the price of medicines. In France, prices of pharmaceuticals are much lower with generics accounting for greater market share. In the past, French pharmacies were better compensated for dispensing more expensive drugs that were more aggressively marketed. Similar to doctors in China, doctors in France favored newer antibiotics such as broad-spectrum cephalosporins, while German doctors favored more generic narrow-spectrum antibiotics. Antibiotic consumption in Turkey has recently increased markedly, closely related to a new reimbursement policy following social insurance reform, a measure that facilitated antibiotic prescription and consumption.[169]

Immigration status, not ethnicity per se, appears to contribute to variation in pharmaceutical use. In a Dutch study, first-generation non-Western immigrants received more antibiotics than the native Dutch (OR 1.31, 95% CI 1.04–1.65), but this effect disappeared in the second generation.[170] A Swedish study found that 8-month-old infants who had both parents born outside of Sweden were more likely to receive antibiotics (OR 1.43, 95% CI 1.24–1.65) than infants with Swedish-born parents.[171] Although Polish, Colombian, Moroccan, and Chinese immigrants to Spain and Norway had lower antimicrobial drug purchase rates than the native-born population, differences (e.g., income, education) related to self-medication and traditional medicine use were not studied.[147]

Regional variation in USA antibiotic use also merit consideration of regional cultural differences as well as practitioner density, demographics, and socioeconomics. Two notable USA trends include correlation of church attendance with both antibiotic and opioid use. A 2014 Pew poll on the religious landscape showed a pattern of church attendance by state (Figure 2, panel C),[172] that was highly concordant with antibiotic-prescribing practices (panel B). It is improbable that receiving antibiotics makes individuals more likely to go to church, or that people who regularly attend church have more infections that require antibiotics. More likely, factors that predispose to church attendance may affect likelihood of taking antibiotics; these need not be exclusive. One such factor may be uncertainty avoidance; church attendance provides a means of coping with uncertainty, since figures of higher authority (be it God, preachers, or doctors) offer solace and reassurance. Another factor might include regional differences in approaches to problem-solving. Regions with high attendance/usage patterns might rely more extensively on externalities -religious belief as an approach for societal and spiritual problems, and medical belief in antibiotics as an approach to bodily problems.

Notably, in the USA, states with the highest antibiotic rates are predominantly Protestant. This is apparently at odds with the hierarchical values hypothesis noted above. Catholicism is more hierarchical than Protestantism and in Europe is associated with higher antibiotic rates.[173,174] However, fundamentalist churches in the Southern and Central US are often led by charismatic preachers who promote authoritarianism.[175] The ethos of these regions has been associated with a high need for security, adversity to uncertainty, fear of contagion, and inclination to support those who provide order and a sense of control,[176,177] characteristics consistent with relatively high antibiotic prescribing.

In the USA, there also is a strong correlation between higher prescription rates for antibiotics and opioid pain relievers in the individual states[178] [Figure 2, panel A]. One possibility is that practitioners who over-prescribe antibiotics provide more prescriptions in general. Since the medications treat entirely different types of problems, this correlation might reflect distribution and type of prescribers providing services, and/or the culture of prescribing, which might be influenced by levels of socioeconomic insecurity and of patient education.[19] Practitioners serving impoverished patients may consider the life circumstances of patients beyond their present illness; antibiotics and pain killers may be prescribed as stop-gap measures for their chronic ill health trajectories. The economics of medical practice also may be relevant, since in many states, a small number of prescribers account for disproportionate opioid prescriptions. The economic considerations may parallel antibiotic-prescribing to avoid losing customers.

Other differences and observations requiring further investigation

A patient's sex is an important variable related to antibiotic overuse. In the USA in 2011, prescription rates for females were almost double those for males.[19] The highest rates were in census tracts with the fewest college graduates, and those with the lowest median income. These data suggest that poorer, less-educated women receive far more antibiotics than do their more-affluent better-educated peers. Does this merely reflect differences in general health, or do other social and cultural factors affect prescribing?

Globally, increases in both Gross Domestic Product (GDP) and physician density have been associated with increased antibiotic consumption in LMICs, but not in HICs, for reasons that are not clear.[2] Another relevant health service consideration is the autonomy of physicians in decision-making or consulting with peers and other health professionals. For example, Belgium, among the European countries with high antibiotic prescribing rates, shares cultural similarities to the neighboring Netherlands where antibiotic use is low,[157] but structural differences in health care system organization may be relevant. The Netherlands, unlike Belgium, has a system of family physician peer-review groups that encourages collaboration and auditing with pharmacists. However, consultations about respiratory tract infections are higher in Belgium than the Netherlands, and differences in prescribing quality are notable.[179]

In several European countries, religious affiliation and church attendance has been declining.[180] Might this reflect on antibiotic usage? An analysis of European countries showed that atheists consumed fewer antibiotics per capita than those in the same country with a religious affiliation. However, atheists harboring more distrustful attitudes had higher rates of antibiotic consumption.[152] A related issue to consider is the impact of vaccination coverage on antibiotic use. Vaccination coverage rates correlate with antibiotic use globally; the proportion of children being vaccinated for measles has been inversely associated with antibiotic consumption.[2] This could reflect direct and indirect vaccine impact on children's health,[181,182] or may mirror broader medical practices. Although these are correlations, they generate hypotheses about the impact of ideology, trust, and authority on behavior related to medicines at individual and population levels. [183,184]

Finally, the global pandemic of COVID-19 has affected antibiotic usage as it has so many other aspects of healthcare. Early in the outbreak, when physicians were faced with severely ill patients with high fevers, even though they knew that the ultimate cause was a virus (SARS-CoV-2), they began empiric antibiotic treatment for suspected bacterial superinfection out of proportion to the real indications.[185] In the moment of crisis, antibiotic use for suspected bacterial infections was the default approach, regardless of indication. Physicians cared deeply for their critically ill patients, and with a dearth of evidence, responded with the now time-honored approach, empiric antibiotics; whether these improved or worsened outcomes was not determined. In some other critically patients, there has been fear of antibiotic toxicity that may be disproportionate to their benefit.[186] Thus, the appropriate use of antibiotics in critically ill patients is complex; fortunately, such patients represent a very small proportion of all of the people receiving antibiotics.

SYNTHESIS AND PROSPECTS

Antibiotics began to be widely deployed in the 1940s, following universal acknowledgment of their salutary properties. Consequently, now >75 years after their introduction, antibiotic use has grown enormously around the world. Antibiotics have become a pillar of contemporary medicine affecting essentially all areas of practice. In this article, we consider six general observations relating to their overuse.

Concepts underlying use variation and overuse

First, the dictum "*Primum non nocere*" (first do no harm), a basic tenet of medicine, demands that potential benefits and risks of any practice must be weighed. Practitioners must use agents when net benefit exceeds net risk. Until recently, antibiotics have generally been perceived to incur minimal risk to their recipients beyond short-term side effects, and medical conditions in which benefits exceed apparent risk have been numerous. In consequence, high proportions of patients are prescribed antibiotics for primary conditions or for prophylaxis. Given current knowledge about antibiotic resistance[2] and antibiotic impact on the microbiome,[14] such practices are now being challenged. The true benefit/risk ratio of antibiotic use for specific medical conditions is being re-examined, and best practice guidelines revised in the face of emerging evidence that remains largely unknown to general practitioners and the public. General patterns of practice substantially lag behind advances in any field.

A growing body of studies now point to substantial previously unrecognized risks associated with antibiotic use. Over the past 15 years, it has become clear that the human microbiome is a central actor in human physiology,[187,188] with many functions deeply integrated into human biology. It has also become clear that the microbiome of people in industrialized countries differs markedly from that of peoples in more traditional societies all over the world, regardless of their location, ethnicity or diet.[189] As cited earlier,[13–16] there now is a wide body of evidence that exposure to antibiotics over these past 75 years is a major factor in these changes. The greatest emphasis has been on antibiotic usage in young children, with respect to altering the microbiome at the very time that host immunological, metabolic, and neural systems are developing [190–195]; and epidemiological studies associate antibiotic exposure with an increased risk of disease of allergic, metabolic, and cognitive disorders that have grown more common in children during the antibiotic era.[196] However, there is increasing evidence in adults that antibiotics also may enhance risk for metabolic and neoplastic diseases, including diabetes, kidney stones,[197] and colorectal adenomas.[198–200] As evidence accumulates about the biological costs of antibiotic use, using knowledge gained from environmental approaches,[201] there is greater need for more rational antibiotic usage. Practitioners have an incomplete understanding about these concepts. Messages about the harm of taking antibiotics typically focus on side effects and drug resistance, but the emerging knowledge of long-term effects on the microbiome has not substantially penetrated the clinical realm. Finally, the concepts that practitioners learned about broad-spectrum and narrow-spectrum antibiotics needs to be brought up to date. These concepts are tied to an antibiotic's ability to suppress common pathogens, but there was no consideration of their effects on the microbiome, which largely is composed of anaerobic bacteria; as such, a "narrow" spectrum agent like penicillin has much deeper effects than a "broad" spectrum agent like ciprofloxacin.[202]

Second, driving overuse is the widespread belief among the general public that antibiotics are beneficial for a broad array of conditions. These extend beyond the treatment of specific illness to disease prevention and even pain management. Perceptions of quality of care by the public often include liberal antibiotic prescribing. The public infatuation with antibiotics both fuels self-use and makes it harder for practitioners to resist the demand to prescribe them.

Third, a general feature of health transition has been a falling threshold of tolerance of illness. People have become less willing to wait and let an illness run its course. The perception that there is a pill for ills of all kinds leads the public to demand immediate relief for symptoms from practitioners and to self-medicate. Antibiotics are widely seen as insuring that an illness will not become worse and be resolved quickly.

Fourth, antibiotic use has become a crutch by those who cannot afford to miss work due to work policies that do not provide paid sick leave. Whether for themselves or for their children in day care, antibiotic use has been used as a quick fix for families that are struggling, when the underlying problems often are related to social inequities. Compounding the problem is that some day care centers exclude sick children for fear of spreading of infection, and demand that they be receiving antibiotics before being readmitted.[203,204]

Fifth, economics matter. The business practices in the competitive health care marketplace operate to generate income. In countries in which antibiotics can only be dispensed by prescription, their availability through the health practitioner brings many potential patients their way, but it carries risk for the practitioner. When patients inappropriately demand antibiotics, practitioners differ in their ability, time, and desire to dissuade patients from unnecessary usage. In competitive medical market places, practitioners are concerned about doctor shopping and the reputational consequences of withholding antibiotics as a means of enacting antimicrobial stewardship,[205] and in countries where antibiotics are commonly purchased over the counter, practitioners are motivated to prescribe "stronger" antibiotics to differentiate from the dispensaries of untrained practitioners and pharmacists.

In LMIC where antibiotics are available without prescription, they often are purchased over the counter, and this wide availability affects prescribing at multiple levels. Pharmacy attendants who directly dispense medicine are privy to the steady stream of prescriptions they see daily, often mimicking the agents used. Pharmaceutical representatives frequently visit doctor's offices and chemist shops, monitor sales, and offer economic incentives for prescribing their products, especially the more expensive agents. An intrinsic conflict of interest exists between optimal care for patient and the financial well-being of the provider. Such issues cannot be fully addressed by regulation, and require greater oversight, professional responsibility, accountability and systems of payment that emphasize keeping people healthy rather than treating disease episodes.

Sixth, lack of continuity of care and time for effective communication lower the trust necessary to convince patients that they do not require antibiotics (or other medications) to recover from illness. With the episodic care that exists on the open market in most locales, incentives are aligned that lead to over-prescribing.

Approaches to solving the problem

It is beyond the scope of this paper to critically review data on the effectiveness of interventions aimed at antibiotic stewardship. Education of both practitioners and the public is necessary, but not sufficient, to deal with the global antibiotic overuse crises we are facing.[206] In closing, we offer several recommendations for those seeking to raise consciousness about the harms of antibiotic overuse and the urgent need to change current practices.

1. Primary care providers need to be convinced that their outpatient practices are in fact contributing to the antibiotic resistance

problem in a substantial way. Antibiotic overuse education also needs to reflect concerns about the microbiome (and related cultural concepts focusing on human ecology) and long-term health promotion and not exclusively on antibiotic resistance. Such messaging needs to be balanced with acknowledging the clear-cut beneficial uses of antibiotics. One solution is to use "social norms" ("how others consider my behavior") as an approach, since such initiatives have reduced smoking behaviors, for example.[207] Employing norms has been used to affect physician behavior,[208] but the results with relation to antibiotic use have been mixed.[209–211]

2. Practitioners must learn about better ways to communicate about antibiotic risks and benefits at levels appropriate to all patients, and to have tools that provide for greater flexibility of prescribing. Providing the necessary information for them will require culturally sensitive translational research that addresses popular misconceptions. The role of the health practitioner as one who carefully evaluates a patient's health status, provides a correct diagnosis, and prescribes medication as needed, should supplant the current dominant role of practitioner as medication dispenser.
3. Communication related to antibiotic overuse must be illness-specific and not just general, consistent with what we have learned in the past about health communication, for both clinicians and patients.
4. Alternatives to antibiotics need to be identified for populations that are highly medicalized and pharmaceuticalized[212,213] and who demand a medication to replace antibiotics, providing the patient with a sense of agency and control. More research is needed about the potential roles or not of probiotics in place of antibiotics.[214]
5. Antibiotics are a common good. Their use is too important to be corrupted by financial incentives. Steps must be taken to eliminate as far as possible, systemic economic factors driving antibiotic overuse at all levels.
6. To address antibiotic overuse, globally as well as locally, it will be necessary to examine social, structural, and commercial determinants of prescription practices, over the counter sales, and self medication.

CONCLUSIONS AND OUTLOOK

The prescribing and use of antibiotics are at the intersection of medicine, economics, and belief systems. Widely considered as "miracle drugs," antibiotics have been overused across the globe, but at differing levels reflecting the confluence of local factors. The increasing knowledge of how antibiotics are affecting the human microbiome will lead to more restraint in their acceptance and in their use. Such changes will not come too soon, because we already are observing extinctions of ancestral taxa that have been linked to the increasing burden of non-communicable diseases happening everywhere. This phenomenon, due to the unintended consequences of human progress, resembles the macro-ecologic process of climate change, but at the micro-ecological level. It is probably occurring at a faster rate than climate change, which is why we must ameliorate antibiotic overuse as soon as possible. We must consider this to be another part of restoring our planetary health; learning from the fight against climate change may provide tools and approaches to gain control. Global variation in human antibiotic prescription and overall utilization *a priori* indicates that use has not been optimized for patient care and societal benefit. It took 75 years to reach the present point of crisis. We are currently at a tipping point; the health and well-being of future generations requires that we reverse current trends of antibiotic misuse. Such action requires recognizing the many drivers of this complex phenomenon and concerted efforts to deal with each in their proper context.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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