Access Barriers to Antibiotics

CDDEP CENTER FOR Disease Dynamics, Economics & Policy
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Related research and additional information on access to antibiotics and antibiotic use and resistance is available at www.cddep.org.

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Acronyms

API	Active Pharmaceutical Ingredient
DDD	Defined Daily Dose
EML	Essential Medicines List
GARP	Global Antibiotic Resistance Partnership
HIC	High-income Country
LMIC	Low- and middle-income Country
NCE	New Chemical Entity
NGO	Non-governmental Organization
OOP	Out-of-pocket
R&D	Research and Development
WASH	Water, Sanitation, and Hygiene
WHO	World Health Organization

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Access Barriers to Antibiotics

Introduction

The emergence and proliferation of antimicrobial resistance have rendered some currently available antibiotics ineffective. Drug-resistant bacterial infections pose a growing mortality threat to populations around the world while many people in low- and middle-income countries (LMICs) continue to die because they lack access to antibiotics (1). The majority of the world's annual 5.7 million antibiotic-treatable deaths occur in LMICs where the mortality burden from treatable bacterial infections far exceeds the estimated annual 700,000 deaths from antibiotic-resistant infections (2,3).

According to recent estimates, thousands of people in LMICs continue to die from treatable pneumococcal infections (Figure 1), and 40.4 million children under the age of five years suffer from treatable acute febrile illness caused by three common bacterial organisms, however only 70% of these episodes are treated with antibiotics (1).

Patients in LMICs are often unable to access antibiotics because they are unable to afford them, and there is limited government expenditure for health services. Furthermore, weak local, national, and international health systems and drug supply chains contribute to the problem of uncertain access. Barriers to access to clinically appropriate antibiotics contribute to increased rates of death due to treatable bacterial infections. In turn, inappropriate antibiotic use futher contributes to drug resistance. As bacterial pathogens, such as those that cause gonococcal infections (Figure 2), become increasingly resistant to common first-line antibiotics, there is need for second- and third-line antibiotics which can be more expensive and may not be available in LMICs. Therefore, the lack of access to appropriate antibiotics not only contributes to high rates of preventable deaths but increases drug resistance which, in turn, serves as a major barrier to effective antibiotic use in LMICs.

Access to medicines has been defined by the World Health Organization (WHO) as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are an hour's walking distance from the home" (4). The WHO identifies the following four factors that determine access to essential medicines:

- Rational selection of medicines,
- Affordable prices,
- Sustainable financing,
- And reliable healthcare and supply systems (5).

This report uses the WHO framework for access to medicines to assess the challenges and barriers to appropriate antibiotic access and use and provides potential solutions.

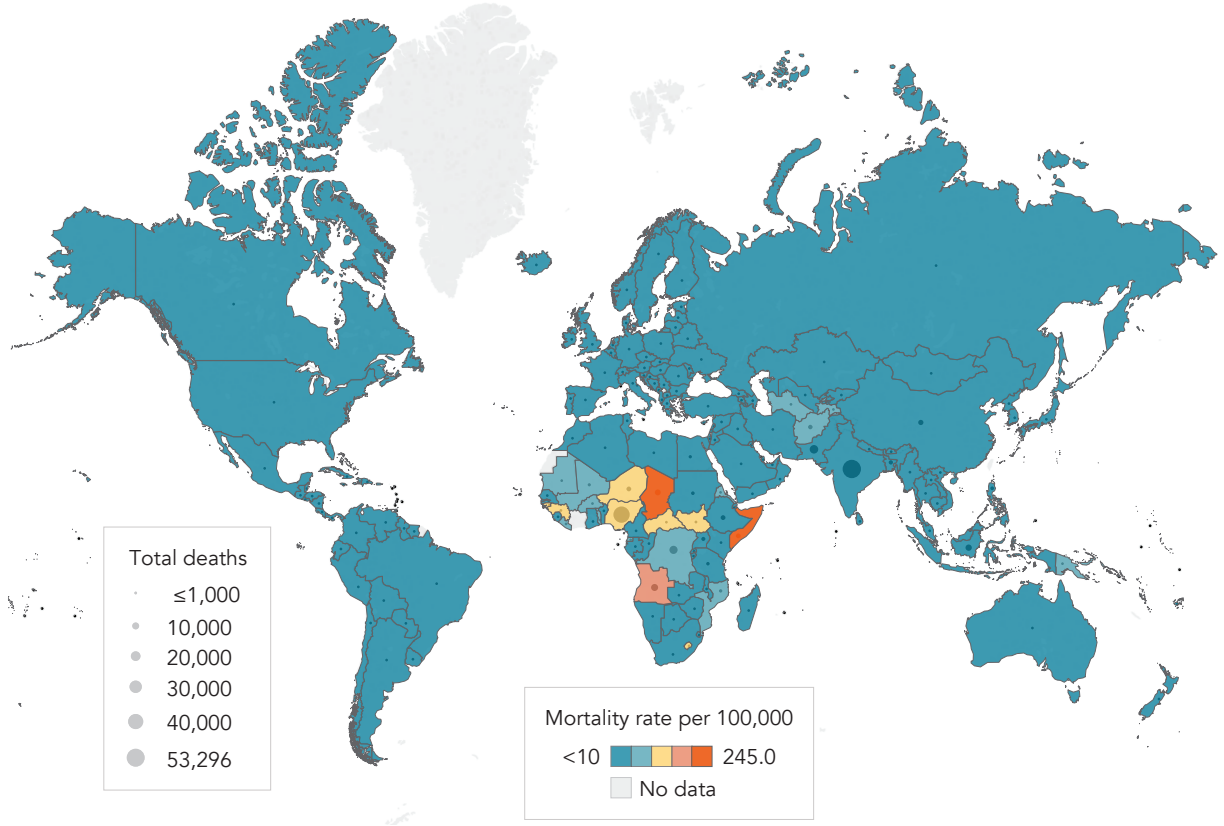

Figure 1. *Streptococcus pneumoniae* deaths and mortality rates per 100,000 (HIV-negative) children aged 1–59 months. Data from Wahl et al. 2018 (6).

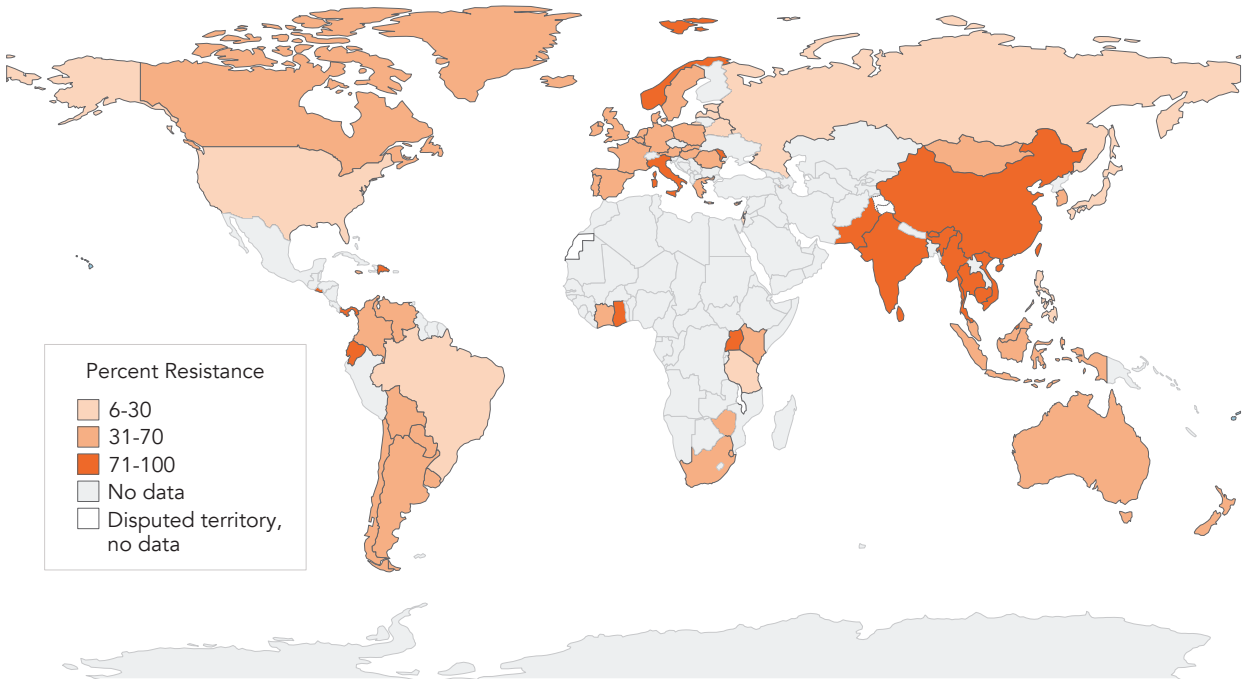

Figure 2. Gonococcal isolates with resistance to ciprofloxacin (data from 2014 for most countries, 2011–2013 for a few countries) Data from Wi et al. 2017 (7).

I. Antibiotic Use in LMICs

Antibiotic use is generally higher in the developed world, but LMICs are rapidly catching up as access to healthcare improves and the burden of antibiotic-treatable infections remains high. Between 2000 and 2015, the global rate of antibiotic consumption increased by 39%, from 11.3 to 15.7 defined daily doses (DDDs) per 1,000 inhabitants per day (Figure 3) (8). (DDD is a statistical measure of drug consumption, defined by the World Health Organization, and is used to standardize the comparison of drug usage between different drugs or between different health care environments.) In LMICs, the consumption rate for cephalosporins, quinolones, and macrolides has increased by 399%, 125%, and 119%, respectively, while in high-income countries (HICs), consumption has decreased by 18%, 1%, and 25%, respectively (8). Particularly worrying is the increase in consumption of new and last-resort antibiotics. Consumption of some second-line agents, such as oxazolidinones, has increased in LMICs and decreased in HICs; however, in many cases, consumption of new and last-resort antibiotics, such as glycylcyclines and oxazolidinones, has increased globally (8).

Changing patterns of consumption are likely to have multiple causes including economic growth, price reductions on patent expiry, and variation in patterns of resistance. In India, the use of cephalosporins has increased because respiratory tract infections, skin and soft-tissue infections, gonococcal infections, and enteric fever are becoming less treatable with penicillins (9).

Increasing access to antibiotics is essential to reduce the infectious disease burden in LMICs. However, all antibiotic use has the potential to select for resistance and must be carefully managed to ensure both that they are deployed when they deliver the best possible value to patients and public health and that they remain effective for the longest period possible.

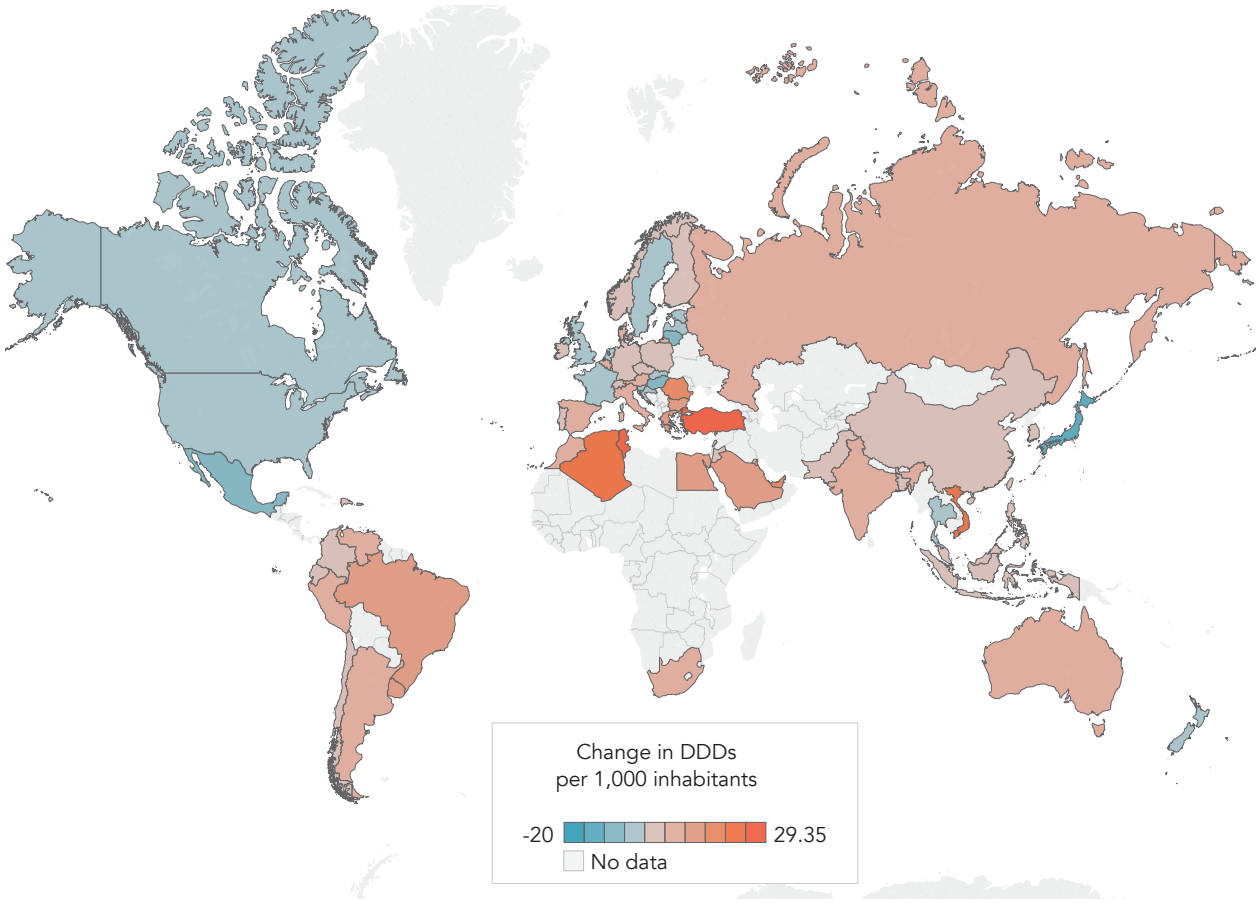

Figure 3a. Global antibiotic consumption (2000 to 2015). Change in antibiotic consumption rate per 1,000 inhabitants per day. For Vietnam, Bangladesh, The Netherlands, and Croatia, change is calculated from 2005, and for Algeria from 2002. Data from Klein et al. 2018 (8).

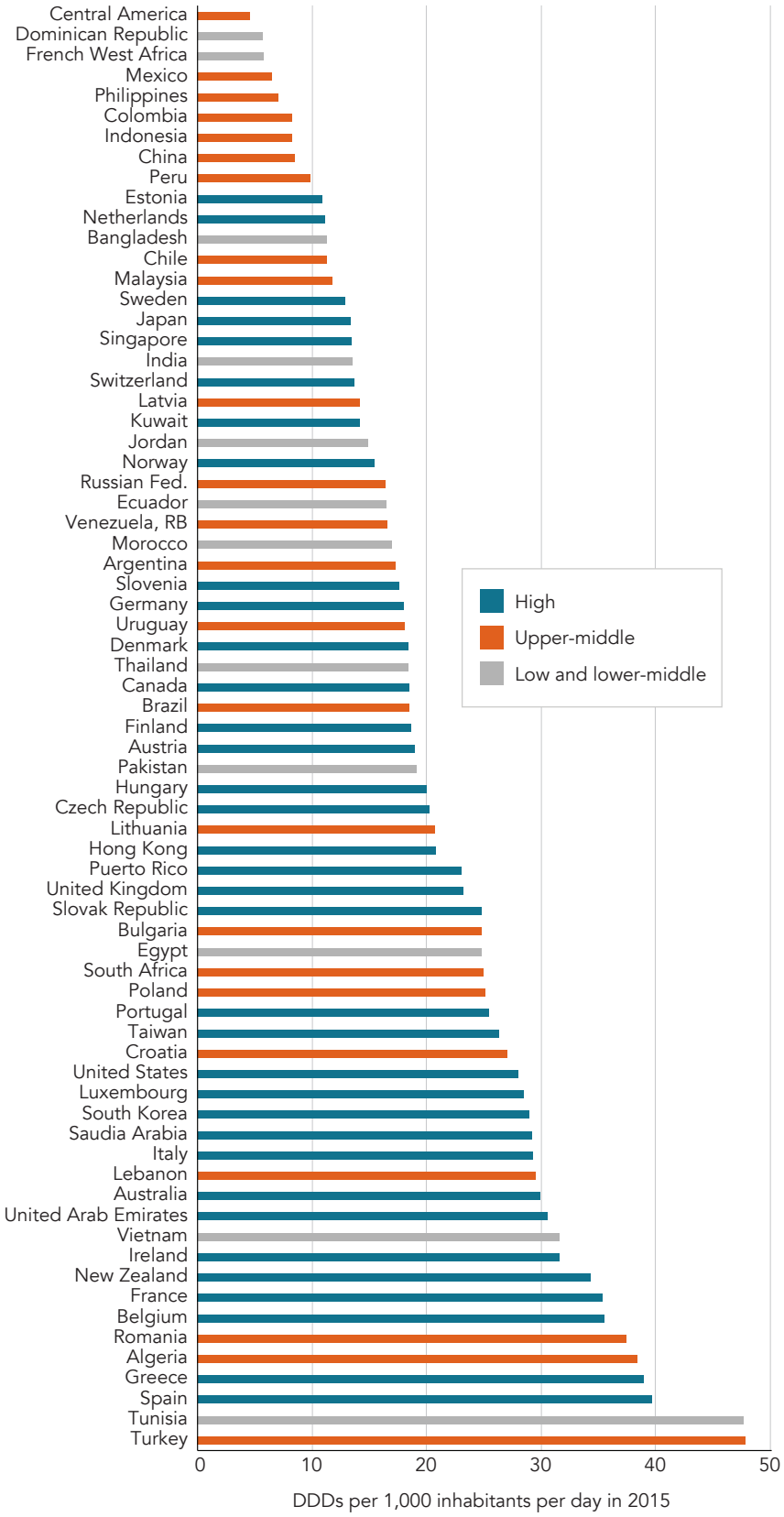

Figure 3b. Antibiotic consumption rate in defined daily doses (DDDs) per 1,000 inhabitants per day by country in 2015. Data from Klein et al. 2018 (8).

II. Barriers to Access

Several barriers to antibiotic access remain. Even though more than 95% of medicines, including antibiotics, on the WHO Essential Medicines List (EML) are off patent (10), in rural primary care facilities in Sri Lanka, for example, just 57% of these medicines are available (11). Access to antibiotics differs by country (Figures 3, 4) and even within regions. Challenges in consistent and reliable access to antibiotics go beyond physical availability or practical affordability; cultural and behavioural barriers persist as well. The main barriers discussed in this report are:

- Weak drug discovery, difficulties in market entry, and poor stewardship leading to irrational selection and use of antibiotics;
- Affordability of antibiotics and inadequate government funding for health resulting in high out-of-pocket (OOP) spending by patients;
- Weak health systems, unreliable supply chains, and poor quality control prevent delivery of antibiotics to patients in need

Our insight into barriers to antibiotic access resulted from a review of the current literature and from interviews with stakeholders in Uganda, India, and Germany, representing low-, middle-, and high-income countries, respectively, as defined by the World Bank (12).

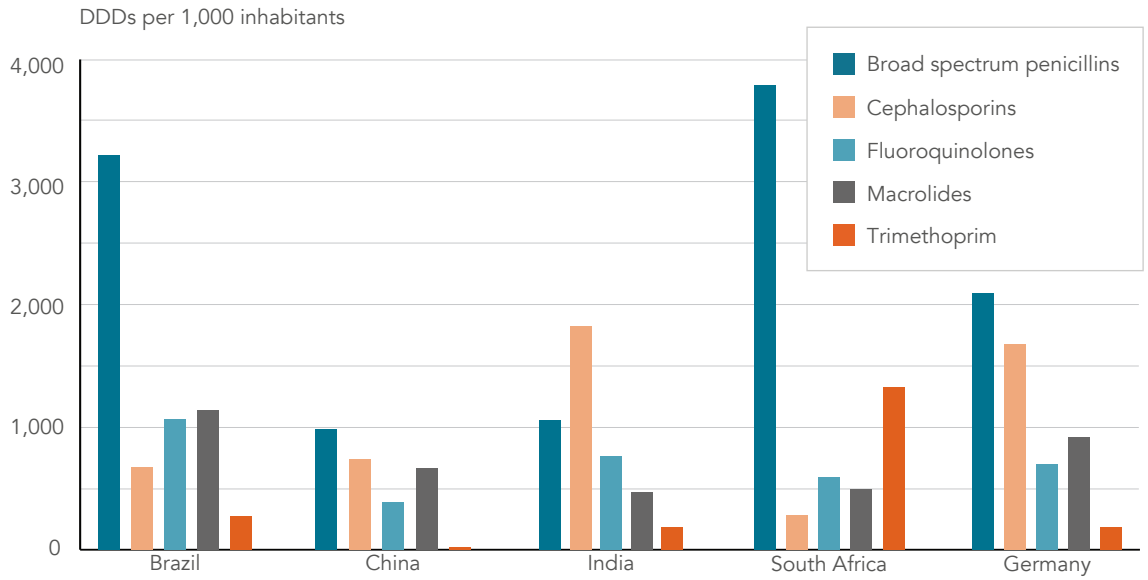

Figure 4. Consumption of antibiotics for selected high- and middle-income countries (defined daily doses per 1,000 inhabitants), 2015. Data available at resistancemap.cddep.org (13).

Barrier 1: Weak drug discovery, difficulties in market entry, and poor stewardship lead to irrational selection and use of antibiotics

Irrational prescribing of antibiotics promotes drug resistance, which causes treatment failure and thereby further reduces access. However, rational selection presumes a portfolio of antibiotics from which the most appropriate treatment can be selected. To properly treat and prevent infections, novel antibacterial treatments are essential as are new vaccines, rapid diagnostic tests, and alternatives to antibiotics; however there are access barriers related to all of these. Though there are exceptions, in many cases, vaccines against bacterial pathogens have proven difficult to develop. Diagnostic tests are of little value unless healthcare providers use the results to inform treatment. Innovation of new antibiotics has slowed since the 1960s; no new class of antibiotic effective against Gram-negative bacteria has been introduced in the past 50

years, though a new candidate raised hopes in late 2018 (14). Some challenges to antibiotic and vaccine development are being addressed; approximately one third of new antibiotics currently in clinical trials are active against Gram-negative bacteria (15), but these drugs are not yet available for treatment.

Still, most antibiotic research and development (R&D) occurs in HICs (16), where patients may have different needs to those in LMICs (3). Even in HICs, investment in antibiotic R&D is considered a market failure due to low sales volumes (particularly for last-resort drugs), short duration of treatment, competition with established products and cheaper generics, and the possibility that resistance will rapidly emerge (17), in addition to scientific and regulatory hurdles (3,18). Of the 20 largest pharmaceutical companies, only five are active in antibiotic research (19). The Global Antibiotic Resistance Partnership (GARP) is one initiative that has proposed ways to address these challenges, perhaps by delinking the cost of R&D from product sales (20).

Even after the discovery of a new antibiotic, regulatory hurdles can delay market entry. Only 12 of 21 (57%) new chemical entities (NCEs) entering markets between 1999 and 2014 were registered in more than 10 countries (21). Nine of these 21 NCEs were registered in just nine markets or fewer, and 90% of countries registered sales of only 2 to 10 of the 21 NCEs (Figure 5). For the majority of these NCEs, market registration began in HICs in North America and Europe (21/25) and then spread through South America, East Asia, and the Pacific and eventually reached the Middle East, Africa, and South Asia. Products introduced over the past six years have, on average, been filed for registration in fewer than five countries per year; in prior years, new products were filed for registration in an average of 25 countries or more (15).

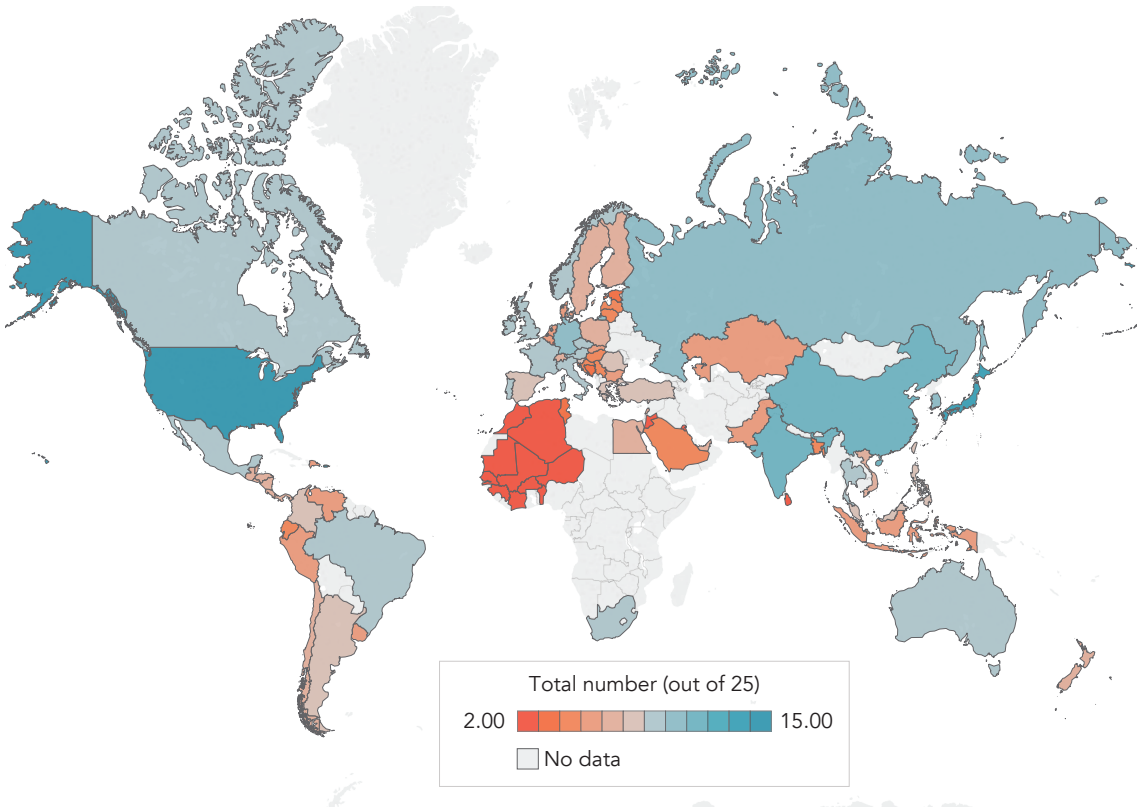

Figure 5. Antibiotic new chemical entities introduced into country markets, 1999–2014. Data for Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama were reported at the regional (Central America) level. Data for Mauritania, Senegal, Mali, Guinea, Cote d'Ivoire, Burkina Faso, Benin, and Niger were reported at the regional (French West Africa) level. Data from Kalberg et al. 2018 (21).

Policymakers have tried to address challenges to market entry for new drugs. For example, the US Food and Drug Administration, European Medicines Agency, and Japanese Pharmaceuticals and Medical Devices Agency have reduced demands for clinical data about drugs targeting indications with limited treatment options (22). However, challenges remain. Recruitment of patients with multidrug-resistant infections for clinical trails is often difficult because prevalence may be low, particularly in specific patient groups (23). Approval requires the demonstration of noninferiority, and the associated difficulties have been well documented (24,25). Requirements for market authorization often differ by country (26). In Africa, pharmaceutical companies must fulfil different technical requirements (e.g., labeling) for individual countries (27), often at substantial cost (28). Approval of amendments to registration documents can interrupt supply chains and cause delays (28). Attempts are being made to harmonize the regulation of medicines in Africa through the African Medicines Regulatory Harmonization Initiative (29). In Japan, the time to authorize a new drug is, on average, 41 months longer than in the United States, depending on the country where the drug was developed (30). The management of safety issues differs by regulatory agency and concerns about safety can lead companies to withdraw products from the market entirely (21).

Pharmaceutical companies can improve access to new antibiotics by planning equitable or tiered pricing strategies and by pursuing registration in countries with high need. Strategies also include commitments to license intellectual property rights to partners in countries where access is limited. Of 28 antibiotics under development in 2017, only four were accompanied by plans to ensure access where needed, and of these, only two plans encouraged appropriate stewardship (15). Because expertise in intellectual property management in LMICs may be limited, countries may not take advantage of flexibilities allowed under international patent law to increase access and affordability of antibiotics to their populations (31).

A generic antibiotic can be marketed after a period of patent and exclusivity protection (32). Substitution of originator brands by generic medicines can save 10% to 90% (33). In the United States, the prices of drugs coming off patent dropped by 40%, 97%, and 95% for ceftriaxone, ciprofloxacin, and citalopram, respectively (34). The price difference between originator brands and the lowest-priced generics in the private sector can exceed 300% in low-income countries; in upper-middle-income countries the price difference can be as high as 152%, while in India it is only 6% (35). Lower prices may lead to increases in consumption (36), but in some cases consumption falls (37). In Denmark, the introduction of generic ciprofloxacin raised consumption; ciprofloxacin resistance subsequently increased (38).

In less regulated markets, as in LMICs, where antibiotics are widely available without prescription and from multiple sources, improved access due to cheaper generic alternatives may reduce consumption of substandard and falsified antibiotics and lower antibiotic use by reducing the burden of disease (27). However, even when cheaper generics exist, they may not be available: across WHO regions, the availability of generic medicines ranges from 58% in Europe to 32% in the eastern Mediterranean (35). Access to generics may also vary between public and private sectors. In Jordan, the availability of generics in the public sector is only 28%, and although the private sector has 80% availability, its generic prices are 10 times higher (35). In LMICs, barriers to implementing effective generic policies include perceptions of low quality, private sector incentives to sell drugs with the high profit margins, the absence of generic substitution policies, and the lack of transparent pricing (39).

Antibiotic use increases selection for resistance, reducing treatment options for resistant infections. Inappropriate prescribing and use by healthcare professionals, medicine vendors, and patients increase the volume of antibiotics used and promote resistance. To promote good stewardship, WHO has classified antibiotics as Access, which should be available in all facilities, Watch, which should be prescribed only for specific indications, and Reserve, which should be saved for cases of last resort (40). Figure 6 compares the sales of antibiotics in these AWaRe categories across selected countries.

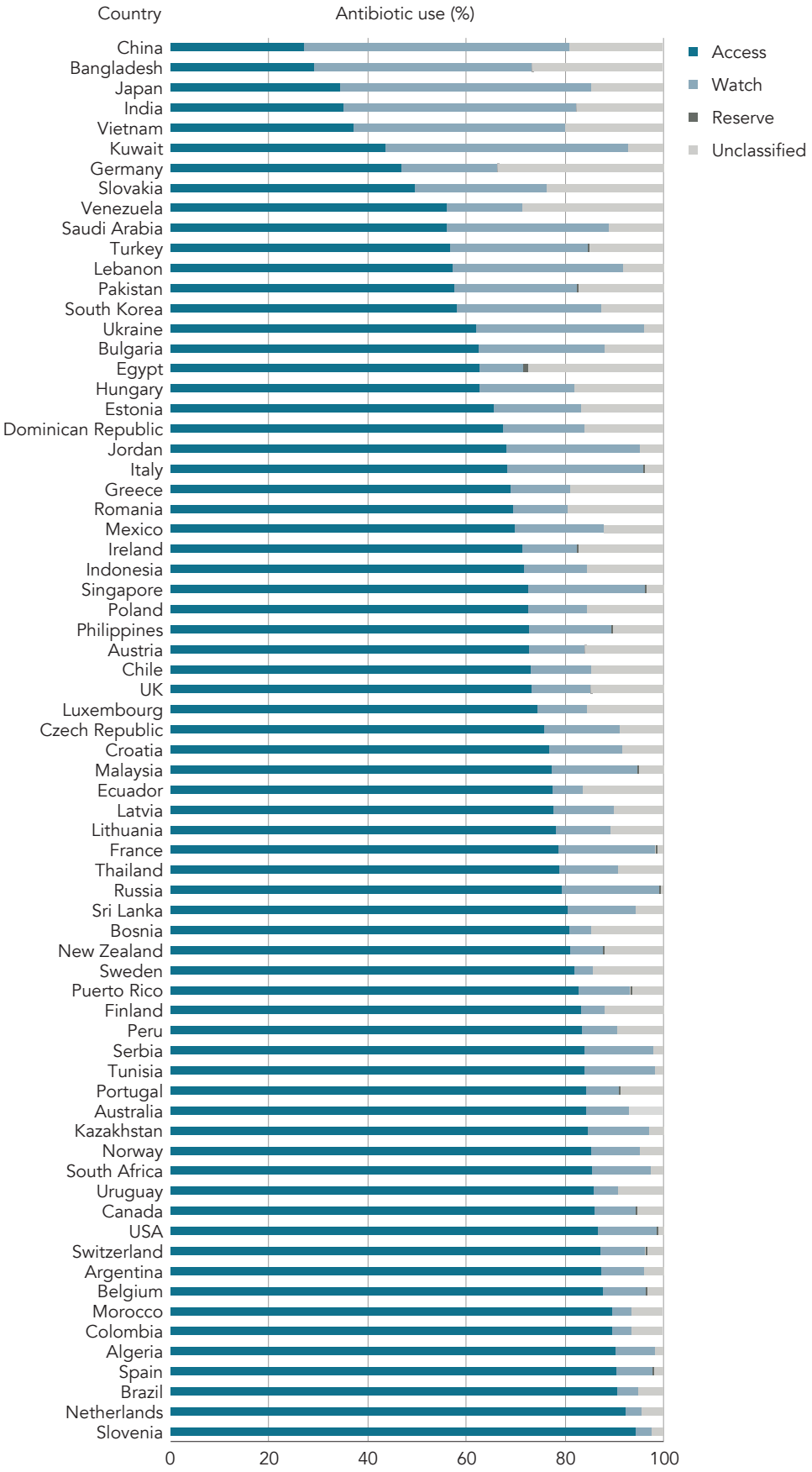

Figure 6. Proportional consumption of oral antibiotic formulations for young children by WHO Access, Watch, Reserve (AWaRe) categorization in selected countries, 2015. Data from Hsia et al. 2018 (41).

The drivers of poor antibiotic stewardship vary. In Uganda, doctors write prescriptions based on availability rather than suitability (42). Similarly, in India, facilities may have a good supply of Watch and Reserve antibiotics but not Access (43). Doctors often prescribe without the results of diagnostic tests, which cost more than empirical treatment, require qualified lab staff and facilities, and are often not reliable (44). For these reasons, diagnostic testing is often considered to provide poor value for the money. A survey in Uganda found that only 26% of laboratories (seven of 27) could provide routine clinical diagnostics and sensitivity testing (45). In rural India, diagnostic facilities are lacking, and pharmacies may not be easily accessible (46). Surveillance data are often not available in low- and middle-income settings (47) and hence the EMLs and standard treatment guidelines are not based on disease prevalence. EMLs and standard treatment guidelines may not be used for procurement, causing shortages of essential medicines (35). In India, most private facilities do not use the EML and may not follow such guidelines.

Healthcare professionals in LMICs may receive limited training in stewardship. In one Ugandan hospital, 42% of patients with no clinical indication for antibiotic therapy received an antibiotic (48). In India, antibiotic fixed-dose combinations are prescribed despite no evidence of an advantage over single compounds; 64% of such combinations had not been approved (49). India's drug regulator, the Central Drugs Standard Control Organization, banned 328 products in 2018 (50); however, past bans have been challenged by the industry (51,52). Interviewees suggested that fixed-dose combinations often allow companies to circumvent price controls on single compound products.

Patients' attitudes may also affect prescribing: in India, some patients prefer intravenous or intramuscular delivery, leading doctors to prescribe according to demand rather than appropriateness. In China, patients showing knowledge of appropriate antibiotic use in physician visits had lower antibiotic prescription rates and drug expenditure (53). In Germany, clinicians can freely prescribe any available antibiotic from the Access, Watch, or Reserve categories, to preserve professional autonomy. Antibiotic prescribing is controlled only where antimicrobial stewardship programs that promote rational use are established in hospitals.

Incentives for the sale of antibiotics promote inappropriate use, and conflicts of interest arise when the sale of medicines is not separated from the remuneration of hospitals and prescribers. For example, in China, hospitals derive significant revenues from the sale of antibiotics, and consequently, antibiotics are prescribed widely and inappropriately (54). Marketers with unrestricted access to healthcare providers in LMICs can influence prescribing (44). In Uganda, for example, doctors can receive financial incentives for prescribing specific brands or using a specific pharmacy. Many doctors have a financial interest in private pharmacies and prescribe more expensive antibiotics even when unnecessary (55). Promoters from pharmaceutical companies encourage doctors to prescribe multiple medications simultaneously and have unregulated access to doctors and pharmacists (55). In India, direct and indirect gifts from medical representatives and commissions influence prescribing practices, and hospitals profit from sales. Doctors feel perceived or real pressure from patients, who, if unsatisfied, may change doctors. Doctors may prescribe for shorter durations than the recommended course of treatment to ensure that the patient returns. Prescribers may prefer to prescribe injectable formulations to maximize their profits (56). In Germany, generic antibiotics dominate the market because hospital contracts drive down prices, but the low prices discourage investment in new antibiotics.

Self-prescribing is common across LMICs. In Uganda, 41% of antibiotic sales are over-the-counter (57). Antibiotics are easily obtained without prescription, and patients may reuse old prescriptions to treat recurrent infections or avoid going to a doctor for infections they consider embarrassing.

In India, Schedule H1 prohibits sales of antibiotics without a prescription but does not include mechanisms for monitoring non-compliance or meaningful deterrents. Nonprofessionals often prescribe or dispense antibiotics. Healthcare providers without formal training provide more than 70% of primary care in India (58). Only 58% of those referring to themselves as doctors in India's cities have a medical degree; in rural areas the proportion is just 19%, and a third of 'doctors' have only a secondary school education (59).

Barrier 2: Antibiotics are not affordable for many in LMICs and government funding for health is low

LMICs face constraints on public spending and have insufficient budgets for healthcare. In Uganda, interviewees indicated that just 8.9% of the national budget goes to health services and only 47% of EML drugs, including antibiotics, are purchased. Government spending on healthcare in India is 1.4% of gross domestic product and insurance coverage is poor. Public health facilities lack adequate medicine stocks, and antibiotic availability is 50% to 60% in some states (60). In India, where 80% of urban healthcare provision is private (61), private retail pharmacies may sell antibiotics at prices higher than the public procurement price (43). Even in Germany, where antibiotics are generally available, newer antibiotics are not on the procurement lists of hospitals because they are considered too expensive. Financial reimbursement mechanisms to support the use of new antibiotics are limited (62), and this may discourage R&D into new antibiotics.

Although global supply shortages have affected even HICs (63), the immediate challenges in LMICs are often associated with supply chain management and budgets for medicines. When stockouts are used as an adverse performance metric, countries may have incentives to keep drugs in stock but not distribute them.

For many patients in LMICs, OOP payments for antibiotics either limit access or push people into poverty (Figure 7). In remote areas, transportation costs for patients and accompanying relatives can be substantial, in some cases exceeding 20% of medical costs (64). In rural Kenya, the main reason for not seeking treatment was "lack of cash." "No drugs available" and "drugs are ineffective" were also stated as reasons (65).

In Uganda, 41% of health expenditure is OOP (66), and 23% of households spend more than 10% of their income on healthcare (67). One study found that 28.8% of respondents were unable to afford all the drugs prescribed to them, 47.8% reported that how much money they had determined the amount of drugs they bought, and only 69.3% said drug prices were within their reach (68). In 2011, Uganda's National Minimum Health Care Package was only 30% funded (69), and because of shortages in public facilities, patients go to private pharmacies or drugstores to buy medicines that should be provided free.

In India, 65% of health expenditure is OOP, versus 13% in Germany (66), and such expenditures push into poverty up to 57 million people each year in India alone (70). Outpatient medicines, mostly antibiotics, comprise a large proportion of these OOP expenditures. Medicines currently account for 77.1% and 70% of OOP payments in Nepal and Timor-Leste, respectively (70). The rollout of universal health coverage in India could improve access for more than 100 million families (71). Antibiotic resistance to first-line treatment, however, compounds the problem of drug affordability by increasing prices as second-line, alternative treatments are more expensive (Figure 8).

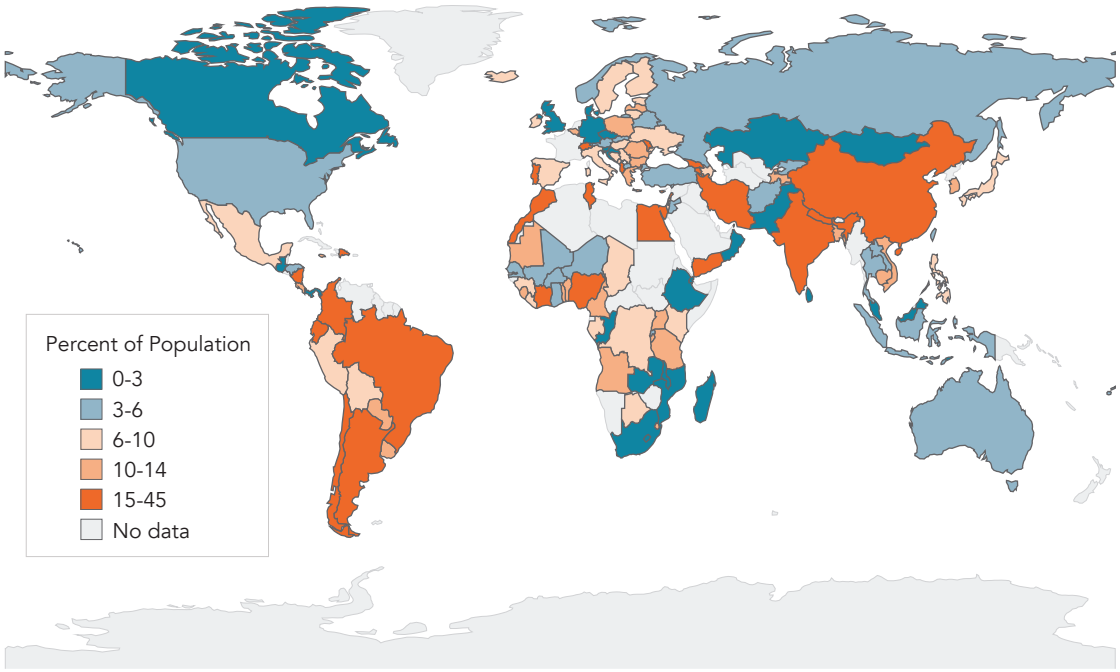

Figure 7. Incidence of catastrophic health spending at 10% threshold, 2016. Data from Wagstaff et al. 2018 (72).

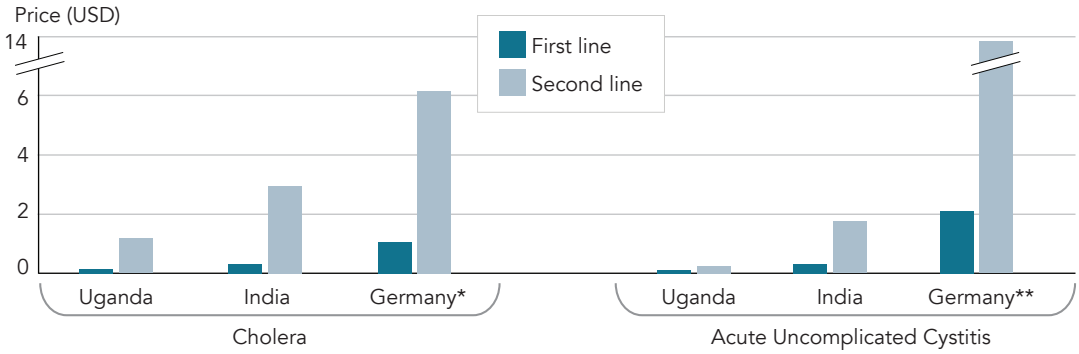

Figure 8. Prices for first- and second-line treatment of cholera and acute uncomplicated cystitis according to national treatment guidelines in Uganda (73) and India (74). National standard treatment guidelines were not available for Germany. *Treatment guidelines for cholera were obtained from (75–77).**Treatment guidelines for acute uncomplicated cystitis were sourced from (78). Prices shown are for selected generic drugs. Prices in Uganda were obtained through consultation with stakeholders and verified through comparison with (79). Prices in India were taken from Monthly Index of Medical Specialties (80). Prices in Germany were sourced from two online pharmacies (81,82). Mean recommended duration of treatment was used to calculate treatment costs.

People in LMICs are often unable to afford essential antibiotics (83,84). For new, patented drugs, one solution is to adjust prices by ability to pay—for example, through the use of pricing tiers within a country (15). However, 95% of medicines on the WHO EML are off patent (10), including the majority of antibiotics. One study in Uganda found that second-line antibiotics can cost 2 to 60 times the price of first-line medicines (85) even though all the drugs included in the study were generic.

Antibiotics in WHO's Watch category are often OOP purchases, and, because of the expense, patients often buy incomplete courses, potentially leading to treatment failure and drug resistance. In India, the same antibiotic may be available in different qualities and formulations in different stores at different prices (a new drug policy has been proposed to change this). The government has capped the prices of 871 essential, scheduled drugs and monitors the prices of nonscheduled drugs. However, government prices are not always the lowest: prices may not be revised as precursor chemicals become cheaper (86,87), and some companies circumvent price controls by varying the formulations.

The lower costs of generics are not always passed on to the consumer. In India, public sector procurement prices of certain older, off-patent antibiotics (including amoxicillin, ampicillin suspension, doxycycline, and erythromycin) were higher than for newer antibiotics (43). The majority of medicines in India's public sector are generic equivalents. The prices charged by private pharmaceutical companies vary significantly, depending on the customer. The lowest-priced generic version of ciprofloxacin in the private sector was three and a half times the price at which the company supplied it to government facilities (86). Pharmacists may substitute the generic drug on a doctor's prescription with a more profitable branded generic or originator drug, to generate a higher profit. Practitioners may prescribe antibiotics for which they receive a commission, raising prices. Hospitals purchase medicines and devices in bulk, sometimes with margins as high as 1,737% (88). In Germany, where patients are covered by insurance, access may be limited by what the regulator is willing to pay. Hospitals are reimbursed using diagnosis-related groups, a combined fee that includes all medication (89). For new treatments, an additional tariff may be granted, but the regulator has not approved requests for new reimbursement fees except for antifungals; hospitals' ability to charge for some newer antibiotics is limited.

Healthcare practitioners' distrust in the quality of generic antibiotics leads to prescribing by brand name, at higher cost to the patient. For example, in Uganda, the presence of poor-quality antibiotics causes doctors to prescribe more expensive branded drugs that patients cannot afford or to double the dose, increasing the incidence of adverse drug reactions (42). Substandard and falsified medicines reduce access to authentic medicines, increase costs for patients and treatment time, undermine physicians' and patients' confidence in healthcare, and can promote resistance to antibiotics.

Profit margins for antibiotics are often low compared with other medicines (63). Manufacturers in low-income countries face multiple hurdles, and local production is often more costly than importation (90). Uganda has few local manufacturers because regulations are stringent, technology and infrastructure requirements for producing antibiotics are expensive, and staffing costs are high. The sourcing of ingredients and labels from WHO-approved suppliers is a challenge, and as environmental controls become stricter, fewer Chinese manufacturers are making inexpensive active pharmaceutical ingredients (APIs), increasing lead times and costs. India has at least 40 API manufacturers and 250 formulation manufacturers (which convert the API into the final product) (91), but this multiplicity can also be problematic by making supply chains inefficient and difficult to manage. The consolidation of purchasing power and, in some cases, suppliers through pooled procurement can lower prices, improve quality assurance, reduce procurement corruption, and increase access to essential medical products (92).

In El Salvador, India, and Mali, among other countries, multiple duties and taxes accumulate across the supply chain and raise prices. Value-added taxes vary from 4% (India) to 15% (Mongolia). In China, Ethiopia, Malaysia, Mali, Mongolia, and Uganda, even the public sector applies retail markups, making medicine sales

a source of government revenue (93). The WHO has suggested that governments and nongovernmental organizations (NGOs) promote pricing transparency throughout the supply chain to raise awareness and empower people (86). Price studies are rare, but markups are common and can be imposed by importers, wholesalers, or retailers (86,94). Optimal prices keep medicines affordable while maintaining a supply chain that is economically viable (93).

Budget constraints cause hospitals and pharmacies to prioritize essential medicines. Watch and Reserve antibiotics are rarely procured. When medicines are not available in time for the fixed administration round times on hospital wards, doses are missed. In India, many health facilities run out of essential antibiotics, forcing patients to purchase high-cost, poor-quality antibiotics from uncertified vendors (95). Purchasing drugs locally leads to avoidable expenses of 410 million INR (US$ 5.9 million) for the Medical Stores Organization (96). Pooled procurement practices have been effective in some states. For example, Tamil Nadu has a constant supply for 100% of the drugs on the EML at prices that are 30% to 40% cheaper than in Bihar (95). Rajasthan, Delhi, Punjab, and Haryana also use pooled procurement.

Interviewees in India suggest that lower profitability, in part potentially due to price controls, on certain antibiotic formulations has led companies to reduce production (91). Injectable antibiotic formulations are more expensive to manufacture, causing shortages in HICs (97). In China, antibiotics have been associated with delays in market reauthorization (98). Of 33 old but clinically useful antibiotics, 24 were available in Germany (99). The absence of older antibiotics is due to high registration costs, small market size, low sales volumes, and low price margins (100,101).

Barrier 3: Weak health systems, unreliable supply chains and poor quality control fail to deliver antibiotics to patients in need

Leadership by the government and health ministries in providing access to essential medicines is often lacking in LMICs. Ill-defined roles, responsibilities, and practices for departments and regulatory bodies compound the problem, and interministerial coordination is a challenge. Insufficient health services at the level of primary care promote antimicrobial resistance ultimately limiting access to effective drugs (102).

In many developing countries, inadequate water, sanitation, and hygiene (WASH) add to both the resistant and the susceptible disease burdens and increase the use of antibiotics that select for resistance. Just 18% of people in low-income countries have access to hand-washing facilities with soap and water (103), and in the least-developed countries, 20% of people continue to defecate in the open (103). Inadequate WASH services cause more than half of diarrheal disease cases, a burden that could fall by 69% to 72% with improved sanitation (104). In India alone, improvements to WASH could reduce the number of diarrhea cases given antibiotics by 590 million by 2030 (104). In short, the burden of infections can be reduced by prevention, and insufficient prevention efforts exacerbate the problem of lack of access to antibiotics.

Health facilities in many LMICs are substandard, and human resources are insufficient or not skilled. In Uganda, 10% to 54% of health staff posts are unfilled because of poor pay, high stress, lack of resources, and poor management (105–107). Staffing on wards is inadequate to administer medicines, patients miss antibiotic doses (42), and public nurses sometimes request compensation for administering medicines. Overall, India has one government doctor for every 10,189 people (the WHO recommends a ratio of 1:1,000), or a deficit of 600,000 doctors (108), and the nurse:patient ratio is 1:483, implying a shortage of 2 million nurses (109,110). These shortages leave patients dependent on informal healthcare providers, especially in rural areas.

Ordering, distribution, inventory management, and storage systems are weak in many LMICs. In Uganda, many products are stored and transported long distances without cold-chain temperature control. Only 47% of medicines on the EML are procured through the centralized authority, resulting in chronic shortages. Public-private-NGO supply chain delivery systems are not leveraged to improve drug availability outside specific programs.

Most manufacturers in the European Union have progressively outsourced production, mostly to companies in China and India. Shortages of piperacillin-tazobactam, ampicillin/sulbactam, and benzathine penicillin were due to API shortages, which in turn were caused by the dependence of supply chains on single, low-cost producers (111). Other shortages have been ascribed to machinery failures, closures of plants, scarcity of ingredients or packaging, spikes in demand, recalls, and parallel imports. The low availability of older antibiotics in Germany feeds a cycle of low demand from physicians and further reduces the perceived market size, making the manufacture of older antibiotics unattractive. Discount contracts between sickness funds and pharmaceutical companies may be contributing to shortages, since many of these contracts are with a single supplier.

Drug quality is also a problem in many LMICs: 17% of the substandard or falsified medicines reported to the WHO are antibiotics (112), and each year, more than 169,000 childhood pneumonia deaths are caused by falsified antibiotics (113). One of the often suspicious antibiotics is amoxicillin, an inexpensive, widely used beta-lactam (114). Poor manufacturing processes include 'tiered production,' whereby manufacturers produce products of lower quality for less regulated markets (115). For example, drugs made by the same Indian manufacturer were more likely to fail API if sold as unregistered products in Africa than if sold in India (116). Authorities face difficulties, however, in proving that production of a substandard medicine is deliberate or that lapses in quality control were criminally negligent. In LMICs the available laboratory capacity is often insufficient to assess drug quality, and regulatory authorities are often not equipped for monitoring and enforcement (117).

The regulation and enforcement of registration, manufacture, sale and quality of medicines are often weak in LMICs. Uganda's regulatory systems are poorly equipped to ensure consistent medicine quality (55), and the country's National Drug Authority has just 80 staff to cover more than 8,000 pharmacies and oversee manufacturing, quality assurance, and wholesale practices for suppliers and distributors. In addition, licensing is a revenue source for the agency, creating perverse incentives to issue pharmacy licenses and not to enforce regulations that forbid the dispensing of antibiotics without a prescription.

In India, regulation is fragmented across states and ministries, and human resources are insufficient. Approval may be easily granted in one state, and once it is granted, the company can market its medicines in multiple states. For private healthcare, there are no national regulatory standards. New generics are not required to have the same bioequivalence and bioavailability as the originator drug, and thus generic drugs may have different pharmacological profiles (e.g., peak concentration reached in the patient, differences in shelf life).

III. Recommendations to Improve Access to Antibiotics

Interventions to improve access to antibiotics must take into account differences among countries. Healthcare institutions, both public and private, and regulatory, procurement, and supply chain systems need to meet users' expectations and clinical best practices. Healthcare in many LMICs requires fundamental changes, more government spending, and better regulation. Countries' long-term visions should include plans to incorporate access to essential antibiotics into priority programs, such as infectious disease surveillance, HIV, tuberculosis, malaria, and mother and child health programs, where efficient supply chains have already been established. National health insurance schemes can reduce out-of-pocket payments by patients, adequately fund health ministries, and dedicate funding for essential medicines, including antibiotics.

Ultimately, rising antibiotic resistance may be the biggest barrier of all. If resistance renders treatments ineffective, efforts to improve access to antibiotics will be futile, and the consequences will be felt worldwide. Antibiotic stewardship and infection prevention must therefore be pursued alongside improvements in access. All stakeholders—international bodies, government leaders, health and agriculture ministries, patients and medical practitioners, farmers and veterinarians, academia, and the pharmaceutical industry—must slow the emergence of resistance to existing antibiotics to ensure affordability and access everywhere.

Barrier 1: Weak drug discovery, difficulties in market entry, and poor stewardship lead to irrational selection and use of antibiotics

	Recommendation	Stakeholder(s)	Rationale
1	Encourage R&D of new or improved antibiotics, diagnostic tests, vaccines, and alternatives to antibiotics for bacterial infections.	Countries, regional collaborations, WHO and other international bodies, pharmaceutical industry, academia	At a global scale, higher investment in novel antibiotics, temperature-stable formulations, and rapid diagnostic tests is needed.
2	Support the registration of antibiotics in more countries according to clinical need.	WHO and other international bodies, national governments, policymakers, regulators, pharmaceutical industry	Efforts at the national, regional, and global levels to support drug registration could reduce the upfront cost of accessing less attractive markets and benefit patients by making life-saving drugs available. Newer drugs coming to market are likely to be introduced by small and medium-size enterprises that may not have the expertise or resources to register in multiple countries. However, this cost should not be a barrier.
		Regulators and policymakers	In many instances, regulations and requirements could be aligned across countries and simplified to reduce costs.
		Pharmaceutical companies	Plans for registration should be part of the development process.
3	Establish standards of practice and national treatment guidelines.	WHO, countries, experts and their professional associations, hospitals and community care facilities	The WHO should issue a call to action for all professional associations and councils involved in prescribing practices to develop clinical guidelines for treating infectious diseases at all levels of healthcare.
4	Generate awareness and educate patients and prescribers.	NGOs, advocacy groups, professional bodies, WHO offices at all levels, health ministries, and local institutions (hospitals, clinics, schools, churches, etc.)	Information about the price and quality of antibiotics approved for use in a country will support rational prescribing and use, as will surveillance data on local antibiotic resistance profiles. NGOs, professional bodies, and advocacy groups can use existing communications channels to educate patients and prescribers about drug quality and rational antibiotic use. Such information will empower consumers who purchase drugs out-of-pocket to demand quality antibiotics while increasing price competition among suppliers and removing poor-quality suppliers from the market.
5	Reduce conflict of interest and incentives that lead to inappropriate antibiotic use.	Regulators, NGOs, doctors, and patients	Conflicts of interest between prescribers and the vendors of pharmaceuticals can be addressed by regulating gifts from drug companies and promoting the enforced or voluntary declaration of such gifts.

Barrier #2: Antibiotics are not affordable for many in LMICs and government funding for health is low

	Recommendation	Stakeholder(s)	Rationale
6	Explore innovative funding of essential antibiotics.	UNICEF/WHO, national governments, pharmaceutical manufacturers	Countries with less purchasing power could pool their resources for procurement under arrangements similar to Gavi (the vaccine alliance) or the Global Fund. UNICEF/WHO might coordinate procurement and distribution. Besides helping LMICs increase their purchasing power, such an arrangement would support quality manufacturers while driving out substandard suppliers.

Barrier #3: Weak health systems, unreliable supply chains and poor quality control fail to deliver antibiotics to patients in need

	Recommendation	Stakeholder(s)	Rationale
7	Ensure the quality of antibiotics and strengthen pharmaceutical regulatory capacity.	WHO, national and regional regulators, countries, pharmaceutical suppliers and manufacturers	With WHO support and coordination, national and regional regulators could collaborate to support quality assurance and avoid duplication of effort across countries. Rapid information exchange for pharmacovigilance, information on poor-quality suppliers, and sharing of best practices and innovation will help drive substandard and falsified antibiotics from the market. An international entity, such as the WHO, could provide surveillance, monitoring, and compliance testing for antibiotic quality. Such work would support LMICs' regulatory authorities and also ensure the integrity of the supply chain from the dominant suppliers in India and China. It could also establish standards for generic antibiotics and fixed-dose combinations, which are commonly used in LMICs, and support the industry in self-regulation.
8	Encourage local manufacturing for cost-effective antibiotics.	Countries, regional collaborations, pharmaceutical industry, including drug R&D and manufacturers	Development and diversification of local manufacturers can help ensure the steady supply of essential, quality-assured antibiotics so that countries can meet their own needs. This should be supported through regional collaborations of countries such as the African Union.

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