# Antibiotic Use and Emerging Resistance

## How Can Resource-Limited Countries Turn the Tide?

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**ABSTRACT**

Antibiotic resistance is a global crisis driven by appropriate and inappropriate antibiotic use to treat human illness and promote animal growth. The antimicrobial resistance epidemic continues to spread due to the triple threat of unfettered access, minimal product regulation and oversight of antibiotic prescription, and lack of clinical diagnostic tools to support antibiotic de-escalation in low-resource settings. In high-resource settings, evidence-based strategies have improved the appropriateness of antibiotic use, limiting the spread of drug-resistant organisms and reducing hospital-associated infections, strategies which may also be effective to stop the spread of resistance in resource-poor countries. Current research and surveillance efforts on antimicrobial resistance and hospital-associated infections in low-resource settings are extremely limited and largely focused on intensive care units. Many challenges exist to improving antibiotic use and infection control in resource-limited settings, and turning the tide requires intensifying research and surveillance, antimicrobial stewardship, and developing new bedside diagnostic tools for bacterial infections and antimicrobial susceptibility.

Since the discovery of penicillin in 1928 by Alexander Fleming, societies have relied on antibiotics in everyday clinical practice. Healthcare providers prescribe these "miracle drugs" to our patients more than any other class of medications, with impressive clinical results and improved patient outcomes [1]. Clinicians and patients rely on antibiotics and are accustomed to having effective antibiotics to cure nearly any bacterial infection.

Though antibiotics are prescribed for an individual patient's condition, unlike other medications, antibiotics have effects that reach far beyond the individual [2]. Even when used appropriately and as prescribed, antibiotics and bacteria resistant to antibiotics seep into our local drinking water sources [3—5] after human, agricultural, and animal use [6] and wastewater treatment [7]. They are also common contaminants of locally produced and imported meat and poultry for human consumption [8—13] acting as direct conduits for causing human illness or colonization. Resistant bacteria have the potential to affect the natural bacterial flora of any person, regardless of who first swallowed the pill or received the injection. Indeed, substantial evidence demonstrates a causal link between widespread appropriate and inappropriate antimicrobial use and the emergence of antimicrobial resistance [14—19].

Antibiotic resistance is defined 1) as the ability of a specific bacterium to survive in the presence of an antibiotic that was originally effective to treat infections caused by the bacterium or 2) as the acquisition of a specific antibiotic resistance mechanism [20,21]. There are 4 major mechanisms of bacterial antibiotic resistance: production of enzymes that inactivate the drug; production of modified targets against which the antibiotic has a reduced effect; reduction of permeability to the drug; and active export of antibiotics using various pumps [22]. Bacteria may be intrinsically resistant to antimicrobial agents or may acquire resistance to $\geq$1 class of antibiotics by de novo mutation or exchange of resistance genes from other organisms. Acquired resistance genes may enable a bacterium to produce enzymes that cleave and destroy the antibiotic, to express efflux pumps preventing the drug from reaching a bacterial intracellular target, to modify the drug's target site and thwart binding of drug to target, or to produce alternative metabolic pathways bypassing the drug's target pathway (Table 1) [22—26]. Antibiotic-susceptible bacteria may acquire new genetic material from antibiotic-resistant strains through conjugation, transformation, or transduction, with simple transposons often facilitating the incorporation of the multiple resistance genes into the genome or plasmids [22].

Though dozens of "superbugs" resistant to antibiotics have made headlines over the last quarter century, clinical microbiologists increasingly agree that multidrug-resistant gram-negative bacteria pose the greatest risk to public health [27]. Resistance in gram-positive bacteria, especially *Staphylococcus aureus* and Enterococcus, also continues to rise, with broad implications for loss of effective treatments for skin and soft tissue infections, urinary tract infections, and pneumonias [28,29], all of which are common healthcare-associated infections (HCAI). Antibiotic resistance is common in HCAI, which are localized or systemic infections that are not present at admission to a healthcare facility but occur while patients are receiving treatment for another condition in the facility [30]. Common HCAI include central line—associated blood stream infections,

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**TABLE 1.** Common antibacterial drug targets and selected mechanisms of resistance, by antibiotic class

| Antibiotic Class | Antibiotic Mechanism of Action | Mechanism(s) of Antibiotic Resistance |
|---|---|---|
| Beta-lactams<br>Penicillins<br>Cephalosporins<br>Carbapenems<br>Monobactams | Interference with bacterial cell wall synthesis | 1. Production of beta-lactamases or extended-spectrum beta-lactamases, which hydrolyze and inactivate drug<br>2. Change/down-regulation of porins (access points through bacterial cell membrane), prohibiting drug entry<br>3. Change in configuration of penicillin binding site (such as encoded by *mecA* gene in MRSA) |
| Glycopeptides<br>Vancomycin<br>Teicoplanin | Interference with bacterial cell wall synthesis | 1. MRSA: accumulation of cell wall fragments that thicken the wall and are capable of binding vancomycin extracellularly; change to several metabolic pathways<br>2. *Enterococcus* and MRSA: acquisition of genes that alter peptide synthesis, reducing glycopeptide affinity |
| Macrolides<br>Chloramphenicol<br>Clindamycin<br>Quinupristin-dalfopristin<br>Linezolid | Inhibition of protein synthesis—bind to 50S ribosomal subunit | 1. Multidrug efflux pump systems that pump the drug out of the cell<br>2. Prevention of leader single amino acid substitutions in the chromosomal dihydrofolate reductase peptide synthesis, stopping transcriptional or translational attenuation |
| Aminoglycosides, tetracyclines | Inhibition of protein synthesis—bind to 30S ribosomal subunit | 1. Expression of aminoglycoside-modifying enzymes<br>2. Prevention of leader peptide synthesis, stopping transcriptional or translational attenuation |
| Fluoroquinolones | Interference with bacterial DNA synthesis | 1. Up-regulating production of enzymes inactivating the antimicrobial agent<br>2. Mutations in DNA gyrase and topoisomerase enzymes involved in RNA production<br>3. Drug efflux pump systems that pump the drug out of the cells |
| Rifampin | Interference with bacterial RNA synthesis | Mutation or duplication of drug target, modification cell permeability |
| Trimethoprim-sulfamethoxazole | Inhibition of metabolism (bacterial folate synthesis) | Single amino acid substitutions in the chromosomal dihydrofolate reductase (as in *S. pneumoniae*) leading to decreased binding of drug |
| Polymixins<br>Daptomycin | Disruption of bacterial membrane structure | Mutations altering cell surface charge |

DNA, deoxyribonucleic acid; MRSA, methicillin-resistant *Staphylococcus aureus*; RNA, ribonucleic acid.
Adapted, with permission, from Tenover [22], with supplemental information from other sources [20,23—26].

catheter-associated urinary tract infections, and surgical site infections [30]. Preventing and treating HCAI should be considered as part of the infection control package when considering solutions to stem the tide of antimicrobial resistance worldwide.

As antibiotic resistance becomes increasingly prevalent and recognized, health providers are in danger of losing effective antibiotics to treat both routine infections and infections caused by antibiotic-resistant organisms. To most effectively address this public health crisis, it is

necessary to understand the history and magnitude of the problem as well as plausible solutions. In this review, we detail the current understanding of global antimicrobial resistance, its detection, how resistance to antibiotics affects treatment choice, and the major factors contributing to the rise of antimicrobial resistance, all with a focus on resource-limited settings. We will then review how lower-income countries can turn the tide on global antimicrobial resistance by emphasizing the need for additional data collection, diagnostics development, and antimicrobial stewardship, and, finally, we discuss which proven strategies may be effective in these settings.

## THE STATE OF THE ART—HEALTHCARE-ASSOCIATED INFECTIONS AND ANTIMICROBIAL RESISTANCE IN LOW-RESOURCE SETTINGS

The global infectious disease burden is disproportionately distributed across countries. The majority of the infectious burden is found in low- and middle-income countries (LMIC) [31] as defined by the World Bank (Table 2). The burden of both antimicrobial resistance and HCAI is high in all LMIC, where pooled infection data suggest HCAI rates ≥3× as high as rates in resource-rich countries [32]. In fact, HCAI, regardless of whether they are associated with high-level antibiotic resistance, are on the rise in LMIC. A recent review [32] highlighted the rise of HCAI in developing countries, whereas other sources have deemed HCAI to be the most frequent hospital-associated adverse event worldwide [33—35].

Though antibiotic resistance is widespread and affects the entire world's population, the effects of antimicrobial resistance are even more significant in LMIC [7]. Patients in resource-limited countries may suffer the most from the increasing prevalence of antimicrobial resistance due to challenges in identifying and diagnosing these infections and lack of second- and third-line antibiotics to treat resistant bacteria. When antimicrobial resistance becomes prevalent in resource-rich clinical practice settings, providers are generally able to select second- and third-line treatments. These therapies are often difficult to obtain in LMIC secondary to high cost and low availability.

Overall, few data are available on antimicrobial resistance in most LMIC settings (Fig. 1) [29,36]. The most comprehensive description of patterns of antimicrobial resistance in low-resource countries is a 2011 review in the *Lancet* by Allegranzi et al. [32], summarizing data from only 28 individual articles representing data on approximately 5,000 organisms. The few scattered studies of reasonable size reporting antimicrobial susceptibility have largely focused on adult intensive care units (ICU). These reports suggest that globally, ICUs are hotbeds of emerging, high-level resistance [37—43]. Such alarming reports merit further study in other countries and healthcare settings.

Outside of the adult ICU, the bulk of antimicrobial resistance research to date in LMIC has focused on infections in neonates, one of the world's most vulnerable populations. To treat infections diagnosed within the first 28 days of life, the World Health Organization (WHO) recommends empiric combination antibiotic therapy with gentamycin and ampicillin, but hospital data from developing countries suggest that up to 71% of *Klebsiella* and 50% of *E. coli* isolates are resistant to gentamycin [44], often limiting effective therapy to the carbapenem class of antibiotics, antibiotics not widely available in Sub-Saharan Africa and many other low-resource settings. These early onset neonatal infections are likely maternally acquired, and parallel studies in LMIC mothers report similar levels of ampicillin resistance, including gentamycin resistance among 60% to 70% of *E. coli* and nearly 100% of *Klebsiella* isolates, in addition to 40% to 60% of other *Enterobacteriaceae* [45]. These levels of gram-negative rod resistance, including extended-spectrum beta-lactamase production, have led countries with access to carbapenems, such as India, to use carbapenems as first-line treatment for neonatal sepsis. However, even countries with access to these advanced antibiotics are not immune to encroaching antibiotic resistance; the emergence of carbapenem-resistant neonatal infections among *Enterobacteriaceae* and *Acinetobacter* in these settings is particularly problematic—such infections are essentially untreatable and associated with high mortality [46]. Compounding the issue, clinicians in most LMIC have limited access to useful diagnostics for bacterial infections outside of research and surveillance activities. Without diagnostic support, LMIC clinicians often lack the ability to diagnose infections caused by resistant bacteria with certainty, leading to uninformed prescribing and complicated treatment decisions.

**TABLE 2.** World Bank definitions of countries by resource distribution

| Gross National Income per Capita 2013 U.S. Dollars | World Bank Classification |
|---|---|
| ≤$1,045 | Low income |
| $1,045 to $12,746 | Middle income |
| ≥$12,746 | High income |

The World Bank country and lending groups are from the World Bank Group (2014) [31].

## ANTIMICROBIAL RESISTANCE—A THREAT TO LMIC, ALSO A GLOBAL PUBLIC HEALTH EMERGENCY?

Resistance to penicillin has been detected in low levels in historical samples of bacteria even prior to its widespread use [47]. This finding illustrates that some mechanisms of resistance occur naturally in the environment and may be enhanced and selected for by antibiotic use, even if the use is appropriate. Other types of drug resistance develop only under direct selection pressure through inappropriate use of antibiotics. Inappropriate antibiotic use can take many forms, including courses of therapy that are either too long

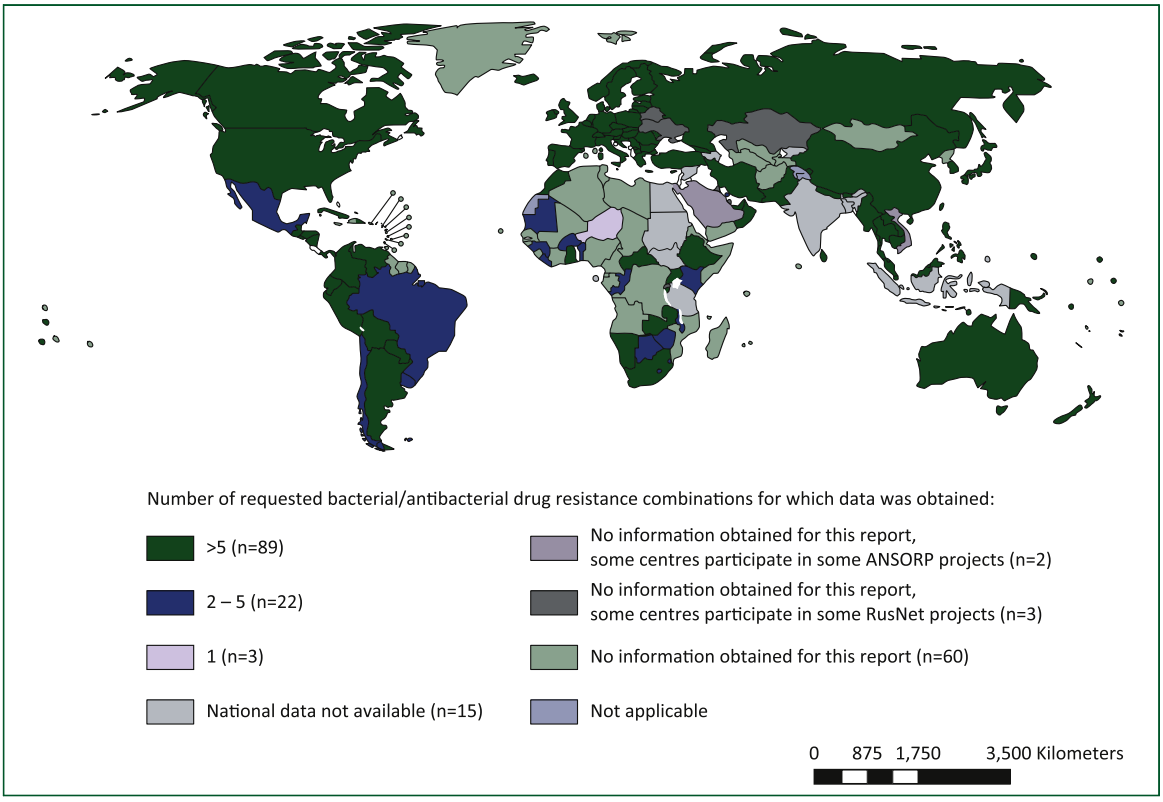


**FIGURE 1. World Health Organization report on availability of data on resistance for selected bacteria-antibacterial drug combinations, 2013** [29]. Number of reported bacteria is based on the information obtained on the basis of request to national official sources on antibacterial susceptibility testing of $\geq$1 of the requested combinations, regardless of denominator data. Data from United Arab Emirates originate from Abu Dhabi only. ANSORP, Asian Network for Surveillance of Resistant Pathogens.

or too short, incorrect dosing, or use of antibiotics when not clinically indicated. Antibiotics are misused in all regions of the world [48].

Whereas mutations conferring resistance are common to all regions of the world, and thousands of individual mutations have been isolated and described, New Delhi metallo-beta-lactamase-1 (NDM-1) mutations found in gram-negative bacteria (see Case in Point section) and similar superbugs are among the most disturbing due to a very limited spectrum of effective treatments. People living in densely populated areas of India and Bangladesh are known to be at risk of infection and colonization with resistant bacteria. But how does mobile, high-level antibiotic resistance affect others who are not living in slum communities, neonates and mothers in LMIC, including urban centers of resource-rich countries? Recent case reports have demonstrated that antimicrobial resistance does not respect borders. For example, Ruppé et al. [49] described European leisure travelers to India who had no contact with the Indian healthcare system, remained healthy throughout their trip and after their return home, and then tested positive for carbapenemase-producing *Enterobacteriaceae* in their stool back in Europe. Such demonstrations prove that it is possible to acquire multidrug-resistant colonizers in the absence of direct selection pressure or healthcare contact. Many examples exist of cross-border resistance; the average person living in resource-rich countries cannot ignore the rising prevalence of antibiotic resistance and the interplay between resource-rich and LMIC nations in promoting the spread of highly drug-resistant organisms. This rapid shift of resistant bacteria as well as the genes conveying resistance may herald the dawn of the post-antibiotic area [50]. Clear evidence is mounting that antibiotic resistance is not a local, but rather a global and highly mobile public health challenge. Our dependence on these medications to treat infections—and expectation that we will always need effective antibiotics to cure infections—means that the rapid rise of high-level antimicrobial resistance constitutes a global public health emergency.

## Case-in-point: carbapenems—antibiotic resistance in mainstream news

The globalization of antibiotic resistance made popular media headlines in 2010 when the *New York Times*

published an article on NDM-1, a broad-spectrum broad-carbapenem-active metallo-$\beta$-lactamase mutation moving from southeast Asia to the United States [51]. NDM-1 mutations are a frightening development in recent medical history, as they confer resistance to some of the most powerful and broad-spectrum antibiotics known. These mutations are becoming more prevalent in *E. Coli* and *Klebsiella* isolates worldwide [52], increasing from 0% in 2001 to 1.4% in 2010 [50]. Acquisition of this mutation by bacteria, as with many beta-lactam—resistance genes among gram-negative bacteria, occurs through a relatively simple horizontal plasmid transfer [53]. These mobile genes on plasmids can rapidly spread through bacterial populations [27], an evolution facilitated by population overcrowding and lack of adequate sanitation. Acquisition of these plasmids by gram-negative rods (GNR) decreases carbapenem effectiveness markedly or eliminates the use of this highly effective antibiotic class all together, sometimes leaving no remaining treatment option. Bacteria expressing the NDM-1 mutation are resistant to nearly all antibiotics including the potent carbapenems, leaving the highly toxic aminoglycoside colistin, and black-box warning—labeled drug tigecycline as the only remaining antibiotics with guaranteed activity [27]. Even though the mutation made headlines in hospitals reporting the bacteria in HCAI, what is especially alarming is the commonness of this superbug mutation among routine hospital surveillance samples and outpatients. A recent study in Bangladesh reported 9% prevalence of NDM-1 mutations among 100 patients seeking care for diarrhea from the Dhaka slums, where the population density is up to 100,000 people per square mile [54], resulting in high potential for human-human transmission of the resistant bacterium. In addition to the potential for transmission between humans in crowded settings with sanitation challenges and contaminated water supplies such as these informal settlements, bacteria carrying NDM-1 mutations have been found in the food supply, including livestock, companion animals, and wildlife [55], which may result from environmental contamination or use of antibiotics as growth promoters [56]. A recent study from New Delhi found NDM-1 mutant bacteria in 4% of drinking water and 30% of ground seepage samples [57], and multiple other studies [58—61] have found that a substantial proportion of healthy children and adults across the world carry the resistant bacterium. A study to be published in the *Lancet* now reports that as many as 95% of adults in India and Pakistan carry some bacteria resistant to beta-lactams, including carbapenems [62]. Highly antibiotic-resistant bacteria have been proven to cross international borders *via* human travelers, insect and animal vectors, water, and farm products [63]. Often, transmission is not noticed, because the bacteria may not lead to clinically significant disease, and routine surveillance does not detect them [63,64]. NDM-1 mutations are a sobering illustration of the prevalence, ease of acquisition, and mobility of potentially devastating antimicrobial resistance.

## GLOBAL FACTORS CONTRIBUTING TO ANTIMICROBIAL RESISTANCE AND INAPPROPRIATE ANTIBIOTIC USE

### Access to antimicrobials and product regulation

Antibiotic use varies widely across the globe within and between low-income and high-income countries. The health systems of most LMIC are challenged by low spending on population-based health programs. In many LMIC, <5% of gross domestic product is spent on health care and many countries additionally suffer from a low healthcare worker to population ratio of <1 for 1,000 people [65]. As a result of low healthcare spending and inadequate staffing, funding priorities have traditionally been focused on the most common and devastating diseases. Monitoring and preventing antimicrobial resistance has not featured among those [66]. However, in many LMIC, rates of hospitalization and antibiotic use are increasing, leading to an overall increase in the amount of antibiotic prescribing (Fig. 2) [48]. Institutional and government policies on antibiotic use in LMIC, though variable, are in general less restrictive than in higher-income countries, leaving antibiotic prescribing practices unfettered and at the discretion of the prescriber [29,48,67]. In LMIC, two-thirds of all antibiotics are sold without a prescription, through unregulated private sectors [48], and data from the WHO database show that approximately 80% of all prescribed medicines in LMIC are dispensed by unqualified personnel [48]. Many countries allow over-the-counter sales of antibiotics and few have a national strategy to contain antimicrobial resistance, as is recommended by WHO [68]. In India, though prohibited by law, over-the-counter sales and use of antibiotics are extremely common [69]. The situation is similar in Vietnam and many

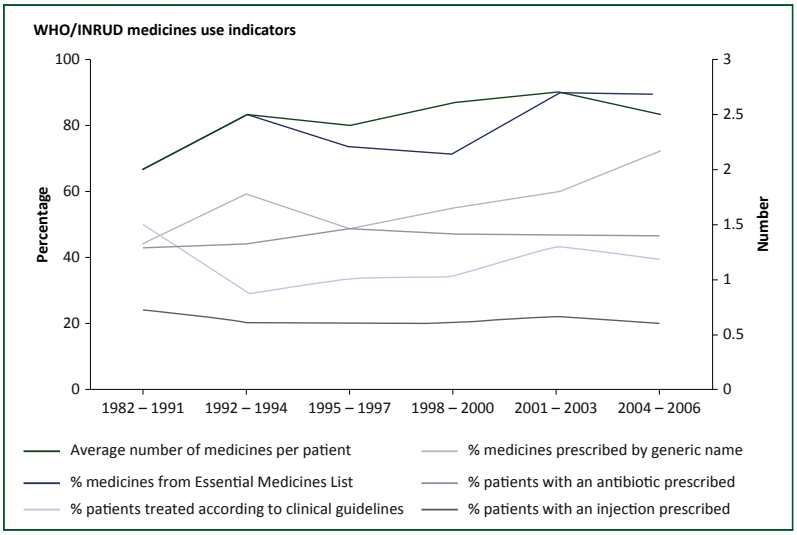


**FIGURE 2. World Health Organization (WHO) report on medicines use in primary care in developing and transitional countries over time, as reported in the *World Medicines Situation 2011* [48].** INRUD, International Network for the Rational Use of Drugs.

other resource-limited countries, where policies often exist to regulate antibiotic use but enforcement is insufficient or lacking [70]. Such unregulated antibiotic use contributes to development of antibiotic resistance [29,48], which is made worse through crowded hospital and clinic conditions and low rates of hand hygiene [71–73].

Data on the relationship between antibiotic use and antibiotic resistance are scarce in LMIC, and few high-quality studies have been published [36]. What is known is that low-resource settings have a higher proportion of antibiotic use [74] and a higher proportion of inappropriate antibiotic prescriptions than high-resource settings [75]. Though the data on antibiotic use and development of bacterial resistance in LMIC are sparse, data in other settings support the correlation between antibiotic use and resistant bacteria, highlighting reason for concern over high, unmonitored antibiotic use in these settings, emphasizing the importance of restrictive antibiotic prescribing policies [76]. A prudent global strategy to reduce the spread of antimicrobial resistance would include increasing restrictions on antibiotic prescribing worldwide.

Restrictions on antibiotic use are difficult to institute. Regulatory policies on antibiotic prescriptions tend to be more common in high-income than in low-income countries [77]. In resource-rich countries, regulatory agencies such as the U.S. Food and Drug Administration and European Medicines Agency restrict entry of antibiotics into the market and ensure high-quality products are distributed in areas under their jurisdiction. In most LMIC, there is little to no oversight of prescribing as described, no standardized antibiogram showing local antibiotic resistance patterns, lack of quality control over production resulting in fraudulent or less than fully potent antibiotics, and limited pharmacy stocks resulting in few readily available choices [48,69]. As of 2007, <40% of all countries worldwide had national policies in place limiting availability of antibiotics to prescription-only [48], with enforcement of these policies occurring almost exclusively in resource-rich settings. There is some evidence that restricting antibiotics to prescription-only does work to improve rational antibiotic use in LMIC. One study from Chile, where a new regulation in 2000 prohibited the dispensing by private retail outlets of antibiotics without prescription, was associated with a significant reduction in overall sales of antibiotics in the private sector [78]. Unfortunately, competing agendas and conflict of interest may make passing and enforcing such regulations difficult. According to WHO, in both 2003 and 2007, approximately 27% of ministries of health reported that revenue from the sale of medicines was used to pay for or supplement health worker salaries, representing a significant incentive for overprescribing [48]. Additionally, added pressure comes from the pharmaceutical industry promoting increased use of its products. Globally, prescribers receive most of their prescribing information from the pharmaceutical industry directly, and in many countries, this is the only information they receive [48].

## Lack of support for clinical decision making

Inappropriate antibiotic use is high in LMIC, and this is exacerbated by a paucity of appropriate diagnostic and clinical tools to assist clinicians in safely de-escalating antibiotics or avoiding their use when unnecessary. The lack of diagnostic assays and equipment is so profound, it has been termed the "Achilles heel" of antibiotic resistance containment [79,80]. Basic diagnostic assays such as routine blood counts to assess for leukocytosis, urinalysis and urinary culture, blood cultures, and plain radiographs are considered essential tools for the practice of modern medicine. Each of these diagnostic tests play a cornerstone role in medical decision making, increasing or decreasing the probability of infection in a patient based on the result. Many resource-poor settings do no offer these tests, or when offered, the tests are too expensive for the vast majority of patients to afford. Furthermore, testing for antimicrobial resistance in bacterial isolates is out of reach in most LMIC clinical practice settings. Where available, microbiologic assays such as the disk diffusion method for antimicrobial susceptibility enable providers to assess for resistance patterns and guide therapy. Without this information, clinicians do not have sufficient information to prescribe the narrowest-spectrum antibiotic needed to treat the patient's disease or to decide that no antibiotic is needed. In addition to the expense of diagnostic technologies and supplies, personnel trained to run the assays are often lacking, and understaffing of LMIC laboratories and microbiology departments is unfortunately too common.

Worldwide, there is general consensus among experts that 50% or more of current antibiotic use could be avoided as unnecessary or inappropriate for the illnesses being treated with antibiotics, without negative consequences to the patients [81]. However, when diagnostic support is not available, clinicians tend to prescribe antimicrobials as a safeguard against severe infection, implicitly calculating that the benefits outweigh the risks for an individual patient. Whereas few studies have examined the impact of basic laboratory and molecular diagnostic tests on detection and therapy for infections, one study performed in sub-Saharan Africa showed that one-third of neonatal meningitis cases could be misdiagnosed without lumbar puncture studies [82]. Such reports underscore why antibiotics may be overprescribed in settings without diagnostic testing; they are a theoretical protection for individual patients. This effect is amplified on a population level, leading to gross antibiotic overuse in settings lacking adequate diagnostic support to de-escalate or stop antibiotic therapy.

Though diagnostic interventions have not been well studied as strategies to reduce antibiotic use in LMIC, it is rational to conclude that the availability of diagnostic testing would lead to more appropriate antibiotic use by providing decision support for clinicians to safely start, de-escalate, change, or stop antibiotics. In LMIC, implementing the same basic laboratory and microbiologic diagnostic assays used in resource-rich settings may be

challenging or impossible for the following reasons: lack of reliable cold chain transport and storage; instability of equipment and reagents in hot and dusty climates; impractical service and replacement contracts; and understaffing or inadequate training of laboratory personnel. This challenge is only exacerbated by the increasing complexity of improved diagnostic equipment, making repairs and upkeep difficult. Equipment service contracts are a necessity, but these may be unaffordable or unavailable in these settings.

Another challenge is that diagnostic technology must be able to keep pace with evolving antimicrobial resistance, a constantly moving target with new resistance mutations and patterns reported regularly. Historically, there has been little incentive for for-profit companies to create rapid diagnostic solutions for low-resource settings, because sales in LMIC may not be lucrative enough to generate adequate return on investment [83]. A possible advantage of the global spread of antimicrobial resistance is that a common bedside testing platform for detection of bacterial infection and antimicrobial resistance profiling could be used in all country settings, leading to higher return on investment through demand from richer countries. Alternatively, affordable devices developed in the LMIC setting could be reverse innovated to be useful in resource-rich settings. The Infectious Diseases Society of America has recently called for the increased development and approval of rapid, accurate microbiologic testing for specific diagnosis of infection, while acknowledging that globalization of diagnostics could be challenging due to varying disease prevalence globally, affecting the pre-test probability of a diagnostic, and limiting its usefulness outside of its intended target area [84]. The ideal characteristics for LMIC diagnostics include low cost, minimal sample preparation requirements, and quick return of results relevant to patient care [84]. The creation of rapid, heat-stable, accurate and simple bedside diagnostics for common bacterial infections is necessary. Such diagnostics could include finger-stick testing for disseminated bacterial infections, allowing for rapid detection of the presence or absence of bacterial antigens with simultaneous genetic analysis of the bacterium for resistance genes. More readily accessible strategies could include use of ultrasound to diagnose pneumonia and transfer of molecular platforms that require minimal sample preparation for bacterial analysis directly to LMIC.

One successful example of dissemination of bedside diagnostic support in LMIC is rapid diagnostic finger-stick tests for malaria. These tests are now in widespread use despite having little application in resource-rich nations. Though necessary, creation and implementation of new diagnostics may not be the panacea. For example, after the introduction of the low-cost, rapid malaria test, which is perfectly poised to help reduce unnecessary antimalarial use, studies showed that some community health workers continued to administer antimalarials in patients despite testing negative [85,86]. Alongside new bedside diagnostics will be the need for extensive education and monitoring and guidance on use once technologies are developed and disseminated.

## TURNING THE TIDE OF ANTIMICROBIAL RESISTANCE: INTERVENTIONS THAT WORK—HAND HYGIENE AND ANTIMICROBIAL STEWARDSHIP

Since its recognition by Semmelweis in the 1800s [87], hand hygiene is judged the most important measure for prevention of microbial transmission during patient care. However, hand hygiene is an irregular practice in low-resource settings, historically reported at rates of <20% [88—90], though new data now suggest that regular hand-cleansing practices may now be on the rise [90—92]. Multidimensional hand hygiene programs incorporating education, observation, feedback, and incentives have been shown to at least transiently improve hand hygiene compliance [90]. To improve hand hygiene globally, WHO developed international guidelines. Implementation studies [93] show that the guidelines have improved overall compliance with hand washing from 51% to 67.2% across all sites where implemented, with greater improvements in LMIC sites than in wealthier nations [93]. Increasing education around hand hygiene practices must be coupled with supplying the means to perform hygiene easily and seems to be a reasonable first step forward in LMIC to control the spread of resistant organisms and reduce HCAI. Importantly, increased hand hygiene has been shown to correlate with a reduction in antimicrobial resistance [94] and HCAI [95].

The ideal infection control program to further stem the tide of antimicrobial resistance and decrease HCAI would pair comprehensive hand hygiene efforts with antimicrobial stewardship. Antimicrobial stewardship programs (ASP) are increasingly considered essential in resource-rich countries, and WHO, Infectious Diseases Society of America, and INICC have called for the development of ASP worldwide [48,67,69,72]. ASP are associated with improved clinical outcomes and reduced antimicrobial resistance [96], achieving their effect through several mechanisms. In general, ASP restrict the use of antibiotics to ones approved by the program, appropriate to their setting as judged by the ASP and then labeled as "formulary" drugs and often acquired and used at lower cost due to bulk purchasing practices. ASP generally require "prior authorization" for clinicians to prescribe restricted or nonformulary antibiotics, making the use of such medications more difficult and also more transparent. Lastly, ASP commonly perform post-prescription auditing, ensuring that the right antibiotics have been used for every infection at an appropriate dose and duration to effectively treat the disease.

Unfortunately, ASP require significant up-front investment in human capital through training. They also depend on specific infrastructure needs, including the ability to perform surveillance on a proportion—if not all—clinical samples, and perform microbiology testing on bacterial isolates to determine resistance patterns. Because

of these requirements, cost can become a barrier to implementation, particularly in low-resource settings. Modified ASP should be considered, which could be scaled-down to the capacity of an individual institution.

Investing in ASP in LMIC is worthwhile, as they have been shown to be effective and cost-saving. A 2012 review summarized recent studies in high-income settings [14], demonstrating in detail the financial offset of implementing an ASP [96,97]. The review described substantial savings sustained over multiyear ASP life spans, showing ASP to be self-sustainable and cost-saving in high-resource settings [15]. One study [97] examined the before-and-after effect from when an ASP was discontinued; it found a temporal association with substantial increased costs driven by higher antibiotic use. Although the cost-savings goals from these programs were moderate, they more than paid for the programs themselves. Similar studies conducted in LMIC could help establish the cost-benefit balance of ASP in these settings. If proven to be as cost-saving or even cost-effective outside of resource-rich countries, it would help motivate resources toward their implementation in LMIC settings. ASP teams in LMIC could have a role in encouraging the switch from intravenous to oral antibiotics based on available clinical and microbiology data, which could lead to substantial savings [97]. Whereas there is a need for consistently available and reliable microbiology and laboratory data to de-escalate therapy safely, it is also possible that ASP teams could safely tailor therapy without such data—a hypothesis worth testing. Once cost savings are established, ideally they could fund additional research and implementation strategies in this area. Given substantial evidence demonstrating a causal link between antimicrobial use and the emergence of antimicrobial resistance [14–19], implementation of ASP in LMIC should, in theory, lead to a significant decrease in antimicrobial resistance over time [98]. There is some evidence to suggest that when specific antibiotic classes are restricted, bacterial resistance selection pressure is lifted, and antimicrobial resistance can once again regress [99], giving hope for ASP to have a significant impact, even in LMIC.

Other interventions routinely used in the high-resource settings to reduce antimicrobial resistance and HCAI in conjunction with a functional ASP include isolation and barrier precautions, selective de-contamination of asymptomatic resistant bacterial carriage, and monitoring and reinforcement of hand hygiene. None of these measures have been studied adequately in LMIC settings, with the exception of hand hygiene monitoring, a recent focus of WHO [89,100]. Each of these potential interventions merits further study in LMIC.

## HEALTHCARE-ASSOCIATED INFECTIONS AND ANTIMICROBIAL RESISTANCE—MORE DATA NEEDED

The bulk of published data reporting high rates of antimicrobial resistance from LMIC are from ICU settings and vulnerable maternal-child populations—but no human population is immune to resistant bacteria. Despite the rapid rise of antibiotic resistance and its potential for global implications, to date, the medical and scientific literature has focused on treatment and management of specific infections, including tuberculosis, malaria, and human immunodeficiency virus. This phenomenon of focus on the "big 3" is especially true in countries where <5% of the gross domestic product is spent on health care and healthcare workforce density is <5 per 100,000 [65]; in these settings, far less attention has been paid to antimicrobial resistance, infection control, and HCAI despite growing implications of these complications. Without this much-needed data, populations and the healthcare systems in these countries, and worldwide, are at risk of high morbidity and mortality due to infections from emerging antibiotic-resistant bacteria.

Where sparse data exist, they often come from small studies with poor data quality, especially data originating from Africa and the western Pacific, 2 of the 6 WHO-recognized world regions [32]. The aforementioned 2011 review and meta-analysis by Allegranzi et al. [32] compiled all data on HCAI in LMIC between 1995 and 2008 and is the most comprehensive review of the topic to date. However, in this study, only 271 studies from LMIC had sufficiently complete data to merit inclusion in the analysis. Furthermore, 54% of those 271 included studies were judged to be of low quality. Among the high-quality studies analyzed in the review, the prevalence of HCAI was 15.5 infections per 100 patients in LMIC, 3× the ratio reported over the same time period in the United States (4.5 per 100 patients in 2002) [32]. Another recent report from a neonatal ICU in Brazil estimated infection density at up to 9× higher than in the United States (15.2 to 62.0 infections per 1,000 patient days vs. 6.9 per 1,000) [32]. These reports strongly suggest that the burden of HCAI in LMIC may be under-recognized, highlighting the need for continued study in this arena.

Despite the significant worldwide burden of antimicrobial resistance and HCAI, very little funding from either public or private sources is available for research (or capacity-building to train professionals) in antimicrobial stewardship and best practices to prevent HCAI. For example, HCAI attracted only 2.0% of U.K. research funding spent overseas, despite constituting a much higher percentage of the worldwide burden of disease [101]. Historically, it has been challenging to justify high-level spending on antimicrobial resistance and HCAI, as data on the incidence and prevalence to drive increased global spending on HCAIs and antibiotic resistance are lacking.

To address the lack of HCAI and antimicrobial resistance data from LMIC, the International Nosocomial Infection Control Consortium (INICC) was created. INICC is an international nonprofit, open, multicenter, collaborative healthcare-associated infection control program with a surveillance system based on that of the U.S. National Healthcare Safety Network [102]. Founded in 1988,

INICC is the first multinational research network established to control and reduce device-associated infections that publishes their research and implementation activities in semiregular manuscripts. In their 2009 report, 173 ICU from 29 countries were included, 68% of which were located in LMIC [64]. Although antimicrobial resistance rates were lower than in U.S.-based ICU for some organisms, rates of high-level carbapenem resistance for *Klebsiella* were nearly 3× higher in LMIC than U.S. ICU [64]. Rates of surgical site infection were also reported to be significantly higher in INICC hospitals compared with U.S. National Healthcare Safety Network data [103]. According to the INICC data, determinants of a high burden of HCAI in LMIC include the following: inadequate environmental hygienic conditions; poor infrastructure; insufficient equipment; understaffing; overcrowding; lack of knowledge and application of basic infection control principles; prolonged and inappropriate use of antimicrobials and devices; and lack of local and national guidelines, policies, and monitoring [32].

INICC requires member hospitals to have an infection control team comprising a physician and an infection control practitioner, and a microbiology laboratory that can isolate and identify aerobic pathogens from clinical cultures and perform in vitro susceptibility using standard methods [102]. The person responsible for surveillance must have had at least 3 years' experience, and in most hospitals, teams had access to electronic data [91,102]. Forty-six LMIC on 4 continents are current members, but there are no countries represented from Sub-Saharan Africa except Nigeria [104]. Low African participation may be due to the personnel requirements for participation. By far the world's poorest region, Africa represents one-seventh of the world's population. It will record the largest amount of population growth of any world region between now and 2050 and is expected to more than double from 1.1 billion today to at least 2.4 billion by 2050, with nearly all the growth in the 51 countries of Sub-Saharan Africa [104]. Given the population growth and with it the likely rise in infectious disease and concomitant disease resistance, Africa will be challenged to increase its contributions and participation in efforts such as the INICC. Research, diagnostic development, and stewardship efforts will need to be increased in this region to develop the capacity for Sub-Saharan Africa to participate in global research and surveillance methods.

More reliable and systematic data—specific to country and setting—including cost-effectiveness of antimicrobial stewardship and how this could be incorporated into LMIC financial strategy are needed urgently globally. These data can inform policymakers and country officials to make appropriate decisions for their setting that will decrease the rate of development of antimicrobial resistance and help protect their populations from infections that they may not be able to effectively or affordably treat [32]. Future research should include data collection on antimicrobial resistance with respect to HCAI, as susceptibility patterns and degree of antibiotic resistance have almost never been included in such studies [32]. The absence of high-quality studies to evaluate antibiotic nonuse or de-escalation using the support of diagnostic tools is also a hindrance to forward progress in changing antibiotic use practices to mitigate the spread of antibiotic resistance. Innovation and research on bedside or point-of-care diagnostics is stymied by the following: inadequate funding to invent new devices and to study the use of old devices in new ways; cost-containment concerns; lack of reliable electricity, clean water, and cold chains necessary for many diagnostics to function; and concerns over adequate training and staffing of personnel. Research on diagnostics and their potential to reduce antibiotic use and assist with appropriate antibiotic selection based on antimicrobial resistance patterns should be an urgent priority. There should also be a call for research into antimicrobial drug resistance globally, with an increased investment from the public and private sector in every sector to combat this global problem.

The profound lack of data on HCAI and prevalence of antimicrobial resistance in LMIC calls for rigorous surveillance to better define the problem. The most effective surveillance would involve horizontally integrated programs including ASP, pharmacy management, microbiology and laboratory quality control, creation and dissemination of standardized antibiograms, and additional decision support tools such as enhanced, accessible bedside diagnostic tools. Encouragingly, WHO has made an effort to highlight the problem. Starting in 2005, WHO announced the first Global Patient Safety Challenge. Since its inception, 88 U.N. member states, 147 resource-limited countries, and 36 resource-rich countries have committed to reducing HCAI by signing up for this endeavor [32,35]. The goal of the Safety Challenge is to ensure that infection control is acknowledged universally as a solid and essential basis toward patient safety and recognize that infection control, including improved hand hygiene among healthcare workers, supports the reduction of HCAI and their consequences. The hope is that the convening power of WHO and its global visibility will help set worldwide priorities and align global healthcare agendas, promoting additional investments in research about and interventions to counteract antimicrobial resistance across all infection types. Most importantly, future research spending in this area will need to be better aligned with the rapidly increasing sequelae of the burden of disease from resistance and HCAI.

## SUMMARY AND A ROAD MAP FOR THE FUTURE

Antimicrobial resistance has emerged as a global problem and a threat to our collective future. Despite being identified as a worldwide public health priority by WHO and other international organizations, data on antimicrobial resistance and hospital-associated infections in low-resource settings remain extremely limited. Without the infrastructure to collect surveillance and antibiotic use

data, the extent of the problem and impact of interventions cannot be accurately measured. Surveillance and research efforts in LMIC should extend to inpatient as well as outpatient settings in LMIC to ensure that antimicrobial resistance is adequately monitored and addressed. Policymakers should consider the model of ASP from developed countries, adapt these models to the resources and needs of LMIC, and test their effectiveness and potential for cost savings. Major difficulties exist for implementation of antimicrobial and resistance surveillance, including the following: lack of expertise in infection surveillance and control practices; inadequate human and financial resources [32]; poor diagnostic infrastructure; lack of equipment and cold chain for appropriate diagnosis and surveillance of antibiotic-resistant infections. Because of these challenging conditions, some aspects of monitoring and intervention will be out of reach for LMIC. However, others are likely to be feasible and should be tested and implemented, including the development of easier and better tools to diagnose bacterial infections and assess for antimicrobial resistance at the bedside, as well as modified ASP.

The solution to increasing antibiotic resistance will require comprehensive antibiotic stewardship in low-income countries as its cornerstone, and this should be done with the financial assistance and collegial partnership of wealthier nations [105], capitalizing on the political and regulatory willpower of international partnerships. Resource-rich nations should share their expertise in development of ASP, train healthcare personnel from LMIC interested in ASP and other interventions, and encourage trained staff to return to their home countries to implement these skills, transferring this learning to their colleagues to create a brighter future beyond the post-antibiotic era.

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