



THE STATE OF THE
WORLD'S ANTIBIOTICS
2015

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Suggested citation

Center for Disease Dynamics, Economics & Policy. 2015.
State of the World's Antibiotics, 2015. CDDEP: Washington, D.C.

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ACRONYMS

ABCs	Active Bacterial Core surveillance (CDC)	FDA	Food and Drug Administration (United States)
AGAR	Australian Group on Antimicrobial Resistance	GAIN	Generating Antibiotic Incentives Now (bill in U.S. Congress)
AGP	Antibiotic growth promoter	GARP	Global Antibiotic Resistance Partnership
ASP	Antibiotic stewardship program	GERMS-SA	Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa
BAPCOG	Belgian Antibiotic Policy Coordination Committee	HCAIs	Healthcare-associated infections
BRICS	Brazil, Russia, India, China, and South Africa	HIV	Human immunodeficiency virus
CARA	Canadian Antimicrobial Resistance Alliance	LMICs	Low- and middle-income countries
CDC	Centers for Disease Control and Prevention (United States)	MOHNARIN	Ministry of Health National Antimicrobial Resistant Investigation System (China)
CDDEP	Center for Disease Dynamics, Economics & Policy	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
CRE	Carbapenem-resistant Enterobacteriaceae	NARMS	National Antimicrobial Resistance Monitoring System (CDC)
DDD	Defined daily dose	NARST	National Antimicrobial Resistance Surveillance Center, Thailand
DNA	Deoxyribonucleic acid	ND4BB	New Drugs for Bad Bugs (European Union)
DRI	Drug Resistance Index (CDDEP)	NDM-1	New Delhi metallo-beta-lactamase-1
EARS-Net	European Antimicrobial Resistance Surveillance Network	OECD	Organisation for Economic Co-operation and Development
ECDC	European Centre for Disease Prevention and Control	OIE	World Organization for Animal Health
EPI	Expanded Programme on Immunization (WHO)	PATH	Promise for Antibiotics and Therapeutics for Health (bill in U.S. Congress)
ESAC-Net	European Surveillance of Antimicrobial Consumption Network	RDTs	Rapid diagnostic tests
ESBL	Extended-spectrum beta-lactamase	SASCM	South African Society for Clinical Microbiology
ESKAPE	<i>Enterococcus</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella</i> spp., <i>Acinetobacter</i> spp., <i>Pseudomonas</i> spp., and ESBL-producing Enterobacteriaceae	RTI	Respiratory tract infection
ESR	The Institute of Environmental Science and Research (New Zealand)	SU	Standard unit
ETEC	Enterotoxigenic <i>Escherichia coli</i>	TSN	The Surveillance Network (United States)
EU	European Union	UTI	Urinary tract infection
FAO	Food and Agriculture Organization of the United Nations	VINARES	Vietnam Resistance Project
		VRE	Vancomycin-resistant Enterobacteriaceae
		WHO	World Health Organization



TABLE OF CONTENTS

EXECUTIVE SUMMARY	8	CHAPTER 3 ANTIBIOTICS IN AGRICULTURE AND THE ENVIRONMENT.....	38
PATTERNS AND TRENDS IN ANTIBIOTIC RESISTANCE.....	8	KEY MESSAGES.....	38
PATTERNS AND TRENDS IN ANTIBIOTIC USE.....	10	ANTIBIOTIC USE IN AGRICULTURE	38
NEW ANTIBIOTICS AND OTHER INTERVENTIONS	10	ANTIBIOTIC RESISTANCE RATES IN FOOD ANIMALS	39
EXTENDING ANTIBIOTIC EFFECTIVENESS	11	REGULATION OF ANTIBIOTICS IN FOOD ANIMALS	43
GLOBAL AND NATIONAL COMMITMENTS.....	12	ANTIBIOTIC-RESISTANT BACTERIA AND RESISTANCE GENES IN THE ENVIRONMENT.....	45
CHAPTER 1 ANTIBIOTIC RESISTANCE IN 2015.....	14	CONCLUSIONS.....	48
KEY MESSAGES.....	14	CHAPTER 4 THE GLOBAL ANTIBIOTIC SUPPLY AND ITS EFFECTIVENESS	50
GLOBAL PATTERNS AND EMERGING THREATS.....	14	KEY MESSAGES.....	50
RESISTANCE RATES AND TRENDS.....	19	CURRENT AND FUTURE ANTIBIOTIC SUPPLY	50
SURVEILLANCE SYSTEMS	22	ANTIBIOTIC RESEARCH AND DEVELOPMENT	51
CONCLUSIONS.....	24	POLICIES FOR ANTIBIOTIC INNOVATION AND CONSERVATION	57
CHAPTER 2 HUMAN USE OF ANTIBIOTICS	26	CONSERVING AND RESTORING ANTIBIOTIC EFFECTIVENESS.....	58
KEY MESSAGES.....	26	ALTERNATIVE AND COMPLEMENTARY APPROACHES.....	58
GLOBAL ANTIBIOTIC CONSUMPTION.....	26	CONCLUSIONS.....	60
INAPPROPRIATE ANTIBIOTIC USE.....	29	CHAPTER 5 WHAT WORKS AT THE COUNTRY LEVEL	62
SETTINGS FOR HUMAN ANTIBIOTIC USE	29	KEY MESSAGES.....	62
CAMPAIGNS TO REDUCE INAPPROPRIATE ANTIBIOTIC USE.....	35	CHANGING NORMS ON ANTIBIOTIC USE.....	62
CONCLUSIONS.....	35	NATIONAL POLICIES TO CHANGE THE NORMS OF ANTIBIOTIC USE.....	62
		CONCLUSIONS.....	67
		REFERENCES	68

EXECUTIVE SUMMARY

Since their introduction into medicine in the 1940s, antibiotics have been central to modern healthcare. Their role has expanded from treating serious infections to preventing infections in surgical patients, protecting cancer patients and people with compromised immune systems, and promoting growth and preventing disease in livestock and other food animals.

Now, however, once-treatable infections are becoming difficult to cure, raising costs to healthcare facilities, and patient mortality is rising, with costs to both individuals and society. Decreasing antibiotic effectiveness has risen from being a minor problem to a broad threat, regardless of a country's income or the sophistication of its healthcare system. Many pathogens are resistant to more than one antibiotic, and new, last-resort antibiotics are expensive and often out of reach for those who need them.

Antibiotic resistance is a direct result of antibiotic use. The greater the volume of antibiotics used, the greater the chances that antibiotic-resistant populations of bacteria will prevail in the contest for survival of the fittest at the bacterial level.

Two trends are contributing to a global scale-up in antibiotic consumption. First, rising incomes are increasing access to antibiotics. That is saving lives but also increasing use—both appropriate and inappropriate—which in turn is driving resistance. Second, the increased demand for animal protein and resulting intensification of food animal production is leading to greater use of antibiotics in agriculture, again driving resistance.

This State of the World's Antibiotics report records the status of this important global resource and provides critical policy analysis on three issues:

- global patterns and trends in antibiotic resistance and antibiotic use in human beings and animals;
- the existing antibiotic supply and the research and development pipeline; and
- interventions that have been shown to help rationalize antibiotic use and are practicable in all countries.

We present a comprehensive country-level policy response, consisting of six strategies, based on the experience of the Global Antibiotic Resistance Partnership (GARP), which has fostered the development of locally driven antibiotic policy in eight countries. The strategies should be particularly relevant for the many countries that have not yet formally addressed antibiotic resistance.

PATTERNS AND TRENDS IN ANTIBIOTIC RESISTANCE (CHAPTER 1)

Evidence from around the world indicates an overall decline in the total stock of antibiotic effectiveness: resistance to all first-line and last-resort antibiotics is rising. The patterns of which bacteria are resistant to specific antibiotics differ

The greater the volume of antibiotics used, the greater the chances that antibiotic-resistant populations of bacteria will prevail in the contest for survival of the fittest at the bacterial level.

regionally and by country, mirroring patterns of infectious disease and antibiotic use.

The U.S. Centers for Disease Control and Prevention (CDC) estimates that antibiotic resistance is responsible for more than 2 million infections and 23,000 deaths each year in the United States, at a direct cost of \$20 billion and additional productivity losses of \$35 billion (CDC 2013). In Europe, an estimated 25,000 deaths are attributable to antibiotic-resistant infections, costing €1.5 billion annually in direct and indirect costs (EMA and ECDC 2009). Although reliable estimates of economic losses in the developing world are not available, it is estimated that 58,000 neonatal sepsis deaths are attributable to drug-resistant infections in India alone (Laxminarayan et al. 2013). Studies from Tanzania and Mozambique indicate that resistant infections result in increased mortality in neonates and children under five (Kayange et al. 2010; Roca et al. 2008).

Resistant bacteria in humans

Methicillin-resistant *Staphylococcus aureus* (MRSA) has declined in incidence in Europe, the United States and Canada over the past eight years, to 18 percent, 44 percent, and 16 percent, respectively (EARS-Net 2014; CDDEP 2015b; Public Health Agency of Canada 2015). It also has begun to decline in South Africa (to 28 percent), where antibiotic stewardship is taking hold (Kariuki and Dougan 2014; CDDEP 2015b) (Figure ES-1). In sub-Saharan Africa, India, Latin America, and Australia, it is still rising (AGAR 2013; CDDEP 2015b), recorded at 47 percent in India in 2014, and 90 percent in Latin American hospitals in 2013 (PAHO, forthcoming).

***Escherichia coli* (*E. coli*) and related bacteria** have become resistant to newer third-generation cephalosporins, indicating that they are difficult-to-treat extended-spectrum beta-lactamase (ESBL) producers. In 2013, in 17 of 22 European countries, 85 to 100 percent of *E. coli* isolates were ESBL positive (EARS-Net 2014). In 2009 and 2010, 28 percent of all Enterobacteriaceae (the *E. coli* family) from urinary tract infections in 11 countries in Asia were ESBL producers, and resistance to third- and fourth-generation cephalosporins ranged from 26 to 50 percent (Lu et al. 2012). In Latin America in 2014 resistance in *Klebsiella pneumoniae* ranged from 19 percent in Peru to 87 percent in Bolivia (PAHO, forthcoming). In sub-Saharan Africa, median prevalence of

resistance to third-generation cephalosporins ranged up to 47 percent (Leopold et al. 2014).

Carbapenem-resistant Enterobacteriaceae (CRE) are resistant even to last-resort carbapenems. In Europe, five countries reported increases in 2013, starting from low levels of less than 10 percent (EARS-Net 2014). In U.S. hospitals, 11 percent of *K. pneumoniae* and 2 percent of *E. coli* were resistant to carbapenems in 2012 (CDC 2013). In Latin America in 2013, resistance of *K. pneumoniae* to carbapenems ranged from full susceptibility in the Dominican Republic to 28 percent resistant in Guatemala (PAHO, forthcoming). In India, 13 percent of *E. coli* were resistant to carbapenems in 2013. For *K. pneumoniae*, 57 percent were resistant in 2014 (CDDEP 2015b).

Clostridium difficile infections are related to antibiotic use: the bacteria are not affected by most antibiotics and therefore proliferate in the human intestine after most other bacteria are killed by antibiotics. *C. difficile* causes an estimated 14,000 deaths per year in the United States (CDC 2013).

Evidence from around the world indicates an overall decline in the total stock of antibiotic effectiveness: resistance to all first-line and last-resort antibiotics is rising.

ResistanceMap, an interactive, data-rich visualization tool, brings together the most current antibiotic resistance surveillance statistics from the United States, Europe, and many low- and middle-income countries (LMICs) (www.resistancemap.org).

Resistant bacteria in food animals and the environment

Poultry, cattle, and swine raised with antibiotics harbor significant populations of antibiotic-resistant bacteria, which are transmitted to humans through direct contact with the animals and through their meat, eggs, and milk (Marshall and Levy 2011). Some proportion of the antibiotics used in agriculture and aquaculture ends up in the broader

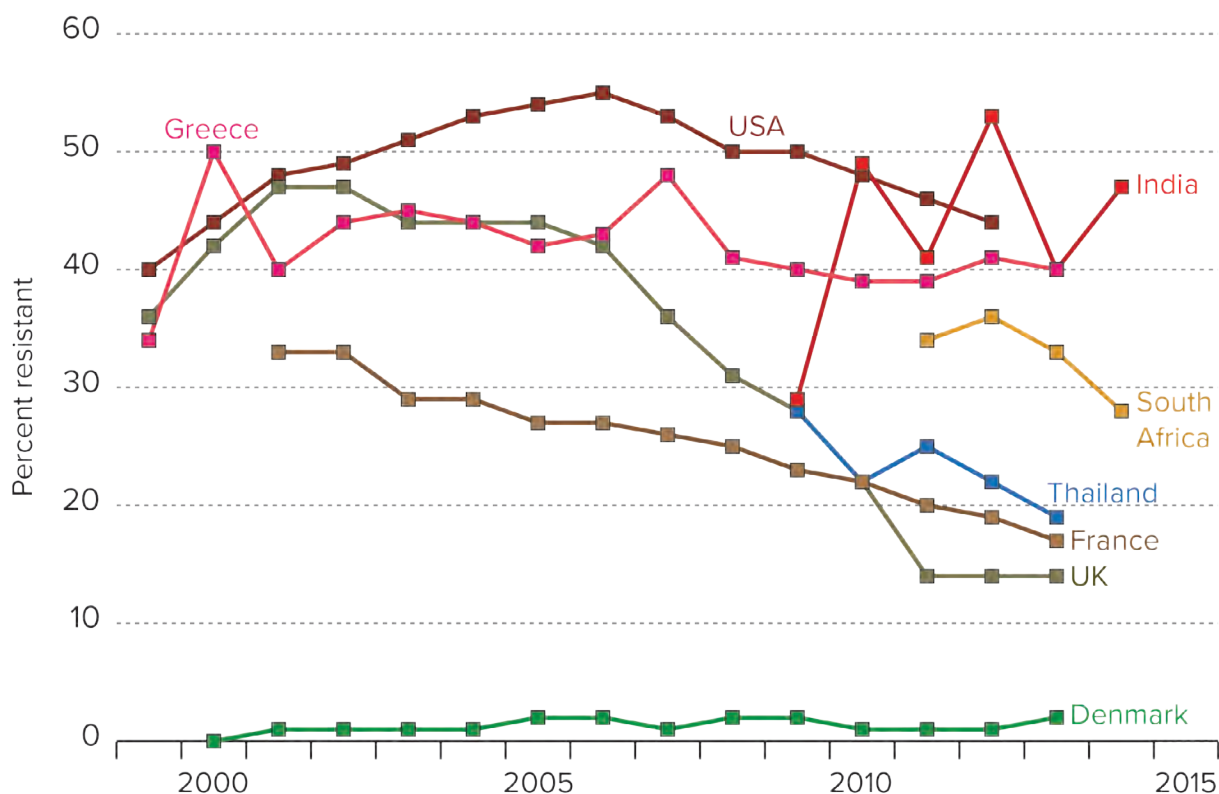


FIGURE ES-11: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

Source: CDDEP 2015

Depending on the country, resistance to one or more of the following drugs may have been used to test for MRSA: Oxacillin, cefoxitin, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant.

¹ CDDEP 2015 sources include: AGAR (Australia), CARA (Canada), EARS-Net (Europe), ESR (New Zealand), NARST (Thailand), SASCM (South Africa), SRL Diagnostics (India), TSN (USA), and VINARES (Vietnam).

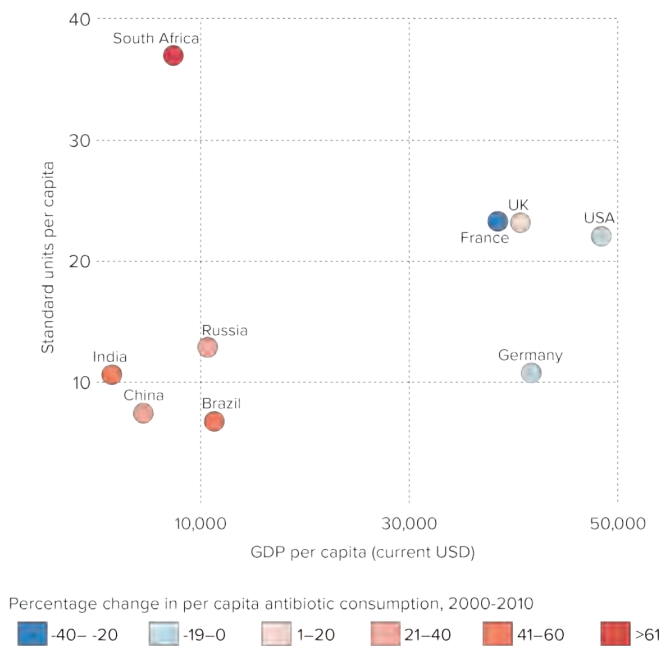


FIGURE ES-2: Antibiotic use per capita by income in selected countries, 2010

Source: Van Boeckel et al. 2014 (based on IMS MIDAS) and World Bank 2015

environment (Daghrir and Drogui 2013), which adds to the total global burden of antibiotic resistance in both animals and humans.

PATTERNS AND TRENDS IN ANTIBIOTIC USE

Human consumption (Chapter 2)

Demand for antibiotics continues to rise, particularly to treat children with potentially fatal sepsis and pneumonia: in 2013, pneumonia was responsible for an estimated 935,000 deaths in children under five worldwide (Liu et al. 2015). If given effective antibiotic treatment, most of these children would not have died.

Between 2000 and 2010, total global antibiotic consumption grew by more than 30 percent, from approximately 50 billion to 70 billion standard units, based on data from 71 countries, including most high-population countries (Van Boeckel et al. 2014). Per capita consumption is generally higher in high-income countries, but the greatest increase in antibiotic use between 2000 and 2010 was in LMICs, where use continues to rise (Figure ES-2).

In most countries, about 20 percent of antibiotics are used in hospitals and other healthcare facilities, and 80 percent are used in the community, either prescribed by healthcare providers or purchased directly by consumers or caregivers without prescription (Kotwani and Holloway 2011). Perhaps half of community use is inappropriate, for coughs and colds that will not benefit from treatment, but it adds to the burden of antibiotic resistance. Hospitals generate some of the most dangerous and difficult-to-treat infections, a result of heavy use of antibiotics (especially in LMICs, where

Demand for antibiotics continues to rise, particularly to treat children with potentially fatal sepsis and pneumonia.

antibiotics may substitute for infection control), immune-compromised and elderly patients, and overcrowding.

Agricultural consumption (Chapter 3)

Increasing prosperity and population growth drive an increasing demand for animal protein. To satisfy this need, many farmers are transitioning to intensive agriculture and often use antibiotics to optimize production.

Antibiotics are used not only to treat individual animals with bacterial infections and prevent infections in herds or flocks, but also to promote growth—a controversial and high-use application. Worldwide, in 2010, at least 63,200 tons of antibiotics were consumed by livestock, likely to be more than all human consumption (Van Boeckel et al. 2015). By 2030, this figure is projected to rise by two-thirds, to 105,600 tons, to meet the demands of a projected 8.5 billion human population (United Nations 2015). Two-thirds of the projected increase is accounted for by increases in the number of animals raised for food production and the remaining one-third by the shift from small-scale to industrial-scale production (Van Boeckel et al. 2015) (Figure ES-3).

Antibiotic growth promotion is the focus of most legal and regulatory efforts to reduce animal antibiotic use because it provides no health benefit to the animals but accelerates antibiotic resistance. Recent analyses suggest that growth promoters have a smaller effect on animal growth than assumed, particularly in production systems that are otherwise optimized (Laxminarayan et al. 2015). The countries with the greatest expected increases in food demand and animal antibiotic use currently have the least efficient farming systems. Emphasis should be on improving productivity without antibiotic growth promoters, as is increasingly the case in high-income countries.

NEW ANTIBIOTICS AND OTHER INTERVENTIONS (CHAPTER 4)

Antibiotics are among the most familiar of medicines and are used liberally by people all over the world. The societal consequence of loss of effectiveness is of little concern to the individual user or prescriber, since resistance affects the next patient. These characteristics combine to foster gross antibiotic overuse and accelerate antibiotic resistance.

Importantly, for at least some antibiotics, resistance levels decrease with declining use, conserving and even recovering some antibiotic effectiveness. In some high-income countries, where antibiotic stewardship has taken hold and public health is good, antibiotic resistance levels have stabilized or declined: when antibiotic use declines, the prevalence of antibiotic-resistant bacteria tends to fall. Vaccines against a range of diseases and improved water and sanitation have moderated antibiotic demand in higher-income countries, and per capita use has begun to level off in many of these countries.

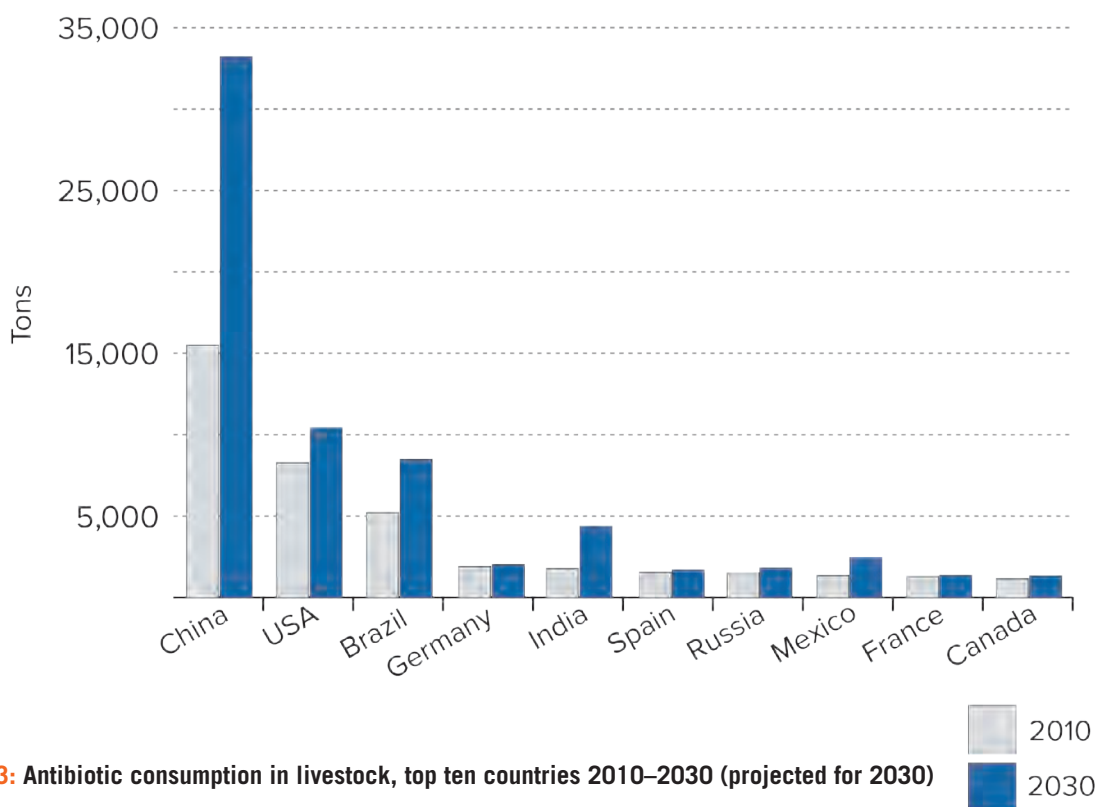


FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

Source: Van Boeckel et al. 2015

The global capacity to treat common infections depends on maintaining an adequate supply of antibiotic effectiveness. Over the past 10 years, the discussion has been dominated by an “empty pipeline” argument, with proposed solutions involving financial incentives for drug developers. Independent analysis suggests that the pipeline is reasonably healthy and has been consistently productive for the past three decades (Outterson et al. 2013) (Figure ES-4). New incentives to spur drug development do not appear to be needed and would do nothing to realign existing incentives for the overuse of antibiotics, nor would they incentivize the development of antibiotics targeted to the most urgent needs. Moreover, new drugs are not widely available in LMICs, where they are unaffordable for patients and healthcare systems (Kariuki et al. 2015).

Feasible, practicable interventions, however, could contribute to maintaining antibiotic effectiveness. Changing the norms regarding how antibiotics are perceived and used requires behavioral change. Alternative and complementary approaches to infection control and treatment, such as improved diagnostic tools, new vaccines, and bacteriophages, will also help maintain the effectiveness of current and emerging antibiotics. Global antibiotic stewardship in the broadest sense should make it possible not only to conserve the current effectiveness of existing antibiotics, but even to reclaim some of effectiveness that has been lost.

EXTENDING ANTIBIOTIC EFFECTIVENESS (CHAPTER 5)

Antibiotic resistance is a global problem, but antibiotic use has its greatest effects locally. It is in every country’s self-interest—for the health of its own population—to prolong antibiotic effectiveness. This means reducing use where

Increasing prosperity and population growth drive an increasing demand for animal protein. To satisfy this need, many farmers are transitioning to intensive agriculture and often use antibiotics to optimize production.

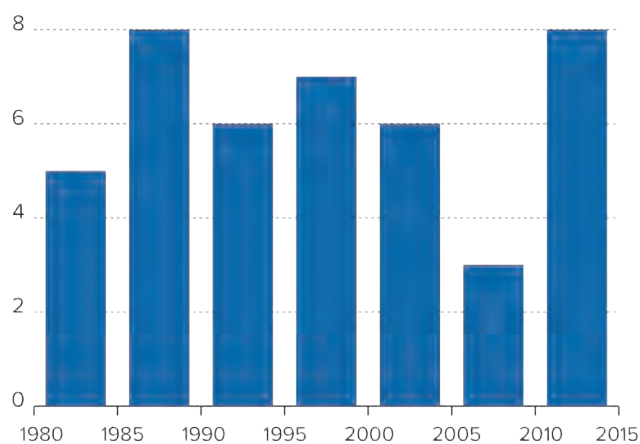


FIGURE ES-4: Systemic new molecular entity (NME) antibiotics still marketed in the US by period of introduction, 1980–2015*

Source: Outterson et al. 2013

*As of August 21, 2015; additional market discontinuations since 2009 are not calculated. Bedaquiline, approved for multidrug-resistant tuberculosis in 2012, is included.

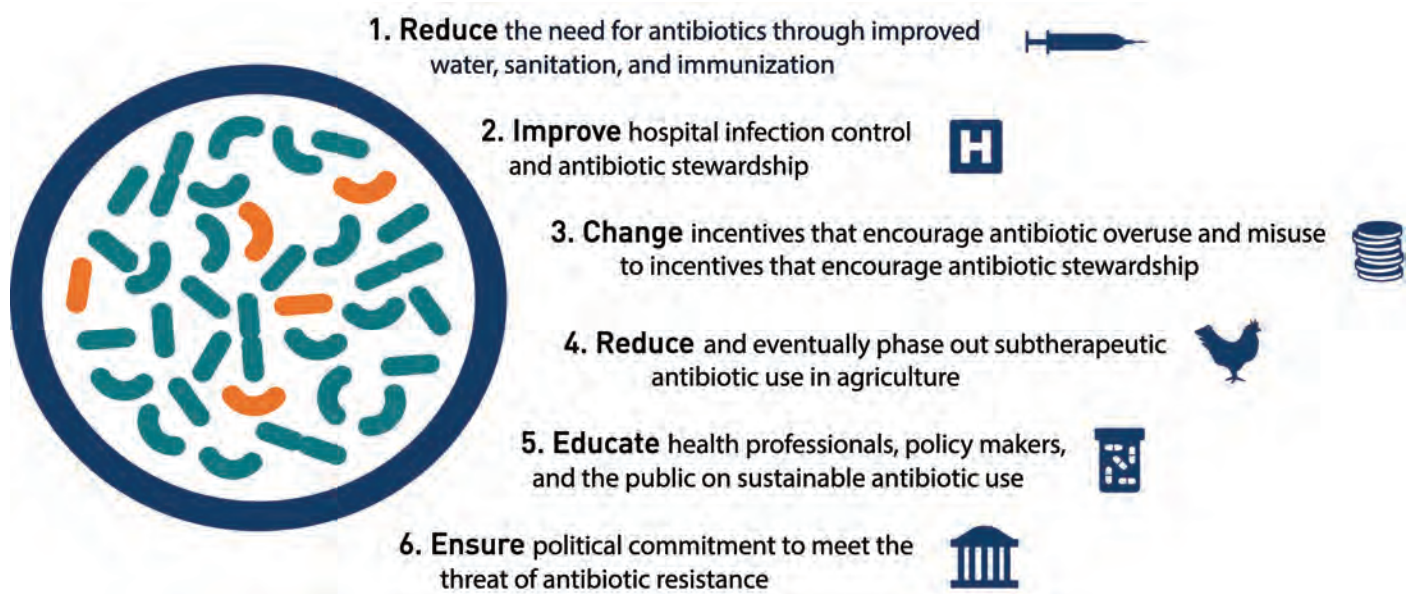


FIGURE ES-5: Six strategies needed in national antibiotic policies

possible and making sure that antibiotics are accessible when needed. Rather than regulating individual actions, however, policymakers should address the mindset about antibiotics. Instead of being the default treatment for a host of mild ailments—particularly coughs, colds, and uncomplicated diarrhea—antibiotics must be considered life-saving medicines to be used when needed.

The transformation will be not easy, but social norms can and do change—witness the change in attitudes toward cigarette smoking. A set of coordinated antibiotic resistance strategies can start the norm-changing process.

GARP has worked with eight countries to establish the capacity and methods for developing antibiotic resistance policies. Six strategies will contribute to slowing resistance and maintaining the effectiveness of current drugs (Figure ES-5):

1. *Reduce the need for antibiotics through improved water, sanitation, and immunization.*
Improving coverage for existing vaccines and adding new ones, improving access to clean water and sewerage systems, and ensuring a safe and healthful food supply all reduce the need for antibiotics, thereby reducing antibiotic resistance rates.
2. *Improve hospital infection control and antibiotic stewardship.*
Better hygiene, particularly hand washing with soap or using alcohol disinfectant between patients, and antibiotic stewardship programs reduce infection rates. Surveillance of resistance and hospital-acquired infections gives administrators information for management and policy decisions.
3. *Change incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship.*
Eliminating economic incentives that encourage the overuse of antibiotics all along the supply chain—in hospitals, in communities, and in agriculture—can conserve antibiotic effectiveness.

Instead of being the default treatment for a host of mild ailments—particularly coughs, colds, and uncomplicated diarrhea—antibiotics must be considered life-saving medicines to be used when needed.

4. *Reduce and eventually phase out antibiotic use in agriculture.*
Eliminating antibiotic use for growth promotion and minimizing use for disease prophylaxis need not jeopardize animal or human health.
5. *Educate and inform health professionals, policymakers, and the public on sustainable antibiotic use.*
Education and guidelines for healthcare professionals, engagement with policymakers, and national awareness campaigns for the public will begin changing the norms in antibiotic use and promote conservation.
6. *Ensure political commitment to meet the threat of antibiotic resistance.*
Presenting the case to policymakers and gaining their political and financial support are critical to success.

GLOBAL AND NATIONAL COMMITMENTS

In May 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance, which calls on all countries to adopt national strategies within two years (WHO 2015). With support from WHO and the international community, this resolution could catalyze change—or, like similar resolutions over the past decade, it may be ignored.

In the United States, the National Action Plan for Combating Antibiotic-Resistant Bacteria (White House 2015) stresses the need to slow the spread of antibiotic resistance through stewardship at all levels. The European Union has taken a similar stance (European Commission 2011). Southeast Asian WHO countries committed to addressing the issue

in the Jaipur Declaration (WHO 2011). The process is also under way in South Africa, started by the work of GARP and continued through a broad coalition of government and private sector leaders.

The evidence in this report, documenting the seriousness of the problem and offering a successful approach to country-level action, supports both the urgency and the feasibility of

making progress in conserving antibiotic effectiveness. The Center for Disease Dynamics, Economics & Policy (CDDEP) will continue collecting reliable data from around the world on antibiotic use and resistance, making the information available to all through ResistanceMap (www.resistancemap.org), and monitoring progress on global antibiotic stewardship.

KEY MESSAGES

- Antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase producers, and carbapenem-resistant Enterobacteriaceae, are increasing in prevalence worldwide, resulting in infections that are difficult and expensive to treat.
- A major driver of antibiotic resistance is antibiotic use, which is fueled by the high background burden of infectious disease in low- and middle-income countries and easy access to antibiotics in much of the world, which increases both appropriate and inappropriate use.
- Few low- and middle-income countries have national surveillance systems for antibiotic-resistant infections. Some, such as India, are beginning to establish networks that will inform clinical decision-making and policy development.

The escalation in the diversity and prevalence of antibiotic-resistant bacteria of the past few years is driven in part by increased antibiotic use in humans and animals and aided by expanded global trade and human movement (Box 1-1). This chapter looks at patterns and trends in antibiotic resistance and describes the surveillance systems that track resistance.

GLOBAL PATTERNS AND EMERGING THREATS

The most recent worldwide estimates of global antibiotic resistance, published by the World Health Organization (WHO) in 2014, list *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* as the three agents of greatest concern, associated with both hospital- and community-acquired infections. In five of the six WHO regions, some countries reported *E. coli* resistance of more than 50 percent to fluoroquinolones and third-generation cephalosporins. *K. pneumoniae* resistance rates to third-generation cephalosporins are above 30 percent in most WHO member countries and exceed 60 percent in some regions (WHO 2014). MRSA resistance rates exceed 20 percent in all WHO regions and are above 80 percent in some regions (WHO 2014).

Streptococcus pneumoniae, nontyphoidal *Salmonella*, *Shigella* spp., and *Neisseria gonorrhoeae* were also identified as community-acquired infections of high global concern. High rates of resistance to first- and second-line drugs are already increasing reliance on last-resort drugs, such as carbapenems (WHO 2014).

This report provides an overview of the best available data on antibiotic resistance rates worldwide, drawing from ResistanceMap (www.resistancemap.org, a global database of antibiotic use and resistance information, developed by the Center for Disease Dynamics, Economics and Policy [CDDEP]), WHO, national sources, and scientific publications.

Methicillin-resistant *Staphylococcus aureus*

MRSA is a common pathogen responsible for skin and soft tissue infections, severe bloodstream infections, and pneumonia. MRSA was once a predominantly hospital-acquired infection but in recent years has been increasingly found in community-onset infections.

The proportion of *S. aureus* that is resistant to methicillin has declined in Europe and the United States over the past eight years, from 22 to 18 percent and from 53 to 44 percent, respectively, though the decrease has been slowing in Europe (EARS-Net 2014; CDDEP 2015b). MRSA rates have also declined in Canada, from 21 to 16 percent since 2009, particularly in hospitals, but remain higher than pre-2000 rates (CDDEP 2015b; Public Health Agency of Canada 2015b). In Australia, MRSA prevalence increased from 12 percent in 2000 to 19 percent in 2013 (AGAR 2012, 2013c; CDDEP 2015b). In sub-Saharan Africa, MRSA prevalence increased in the early 2000s but has decreased since 2011 in South Africa (from 34 to 28 percent) (CDDEP 2015b; Kariuki and Dougan 2014). In India, a steep increase in MRSA, from 29 percent of *S. aureus* isolates in 2009 to 47 percent in 2014 (CDDEP 2015b), was recorded by a large private laboratory network. MRSA prevalence decreased in Thailand from 28 percent in 2009 to 19 percent in 2013 (NARST 2013).

In 2013, MRSA accounted for 90 percent of all hospital *S. aureus* isolates from all but three countries in Latin America

BOX 1-1. MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria resist the effects of antibiotics by using the following genetic strategies, with thousands of variations:

- producing destructive enzymes to neutralize antibiotics;
- modifying antimicrobial targets, by mutation, so that drugs cannot recognize them;
- removing antimicrobial agents by pumping them out (efflux);
- preventing antibiotics from entering by creating a “biofilm” or otherwise reducing permeability; and
- creating bypasses that allow bacteria to function without the enzymes targeted by antibiotics.

Source: Penesyan et al. (2015)

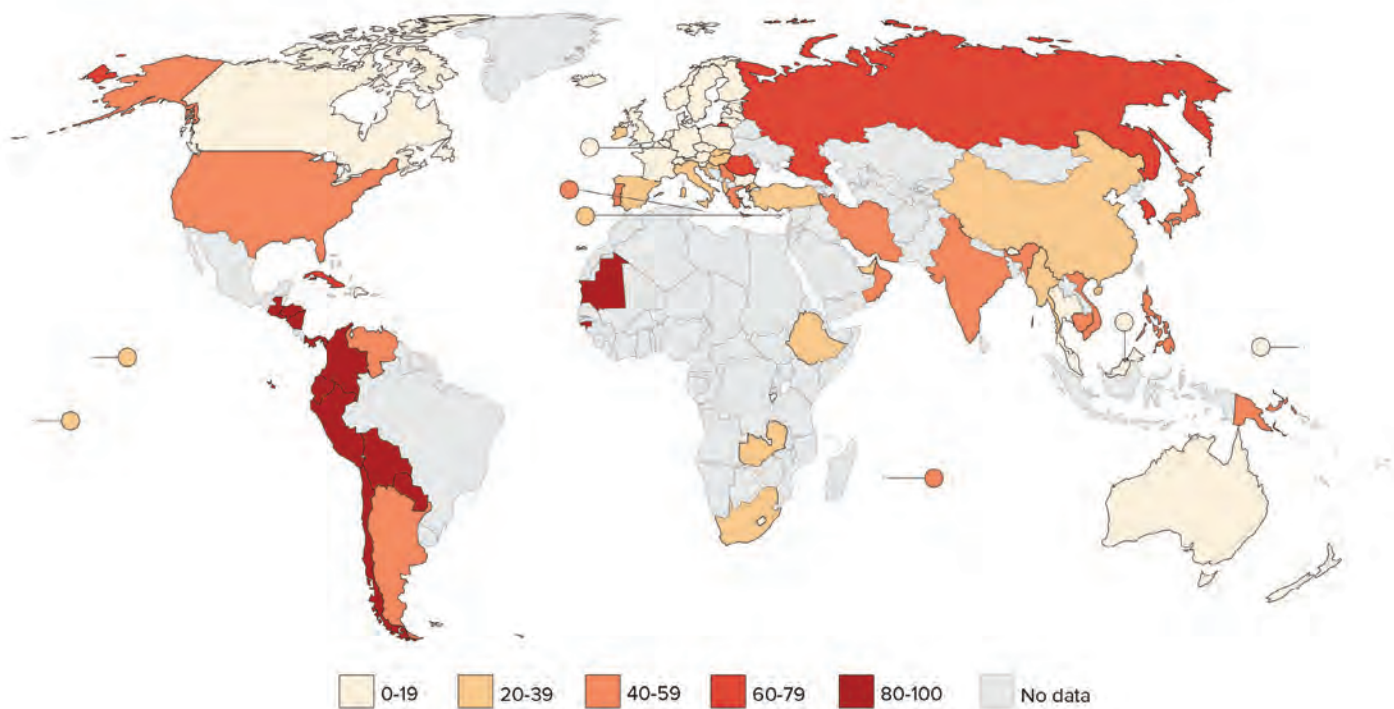


FIGURE 1-1¹: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA), by country (most recent year, 2011–14)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from hospital-associated MRSA and invasive isolates have been used. In their absence, data from community-associated MRSA or all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used to test for MRSA: Oxacillin, ceftaxime, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

¹ The maps in this report display the data for each country from ResistanceMap (CDDEP 2015) and PAHO (forthcoming) as well as nationally representative data from WHO (2014).

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CDDEP 2015 sources include: AGAR (Australia), CARA (Canada), EARS-Net (Europe), ESR (New Zealand), NARST (Thailand), SASCM (South Africa), SRL Diagnostics (India), TSN (USA), and VINARES (Vietnam).

reporting to the Pan American Health Organization, ranging from zero in the Dominican Republic to 100 percent in Chile (Figure 1-1). In community settings, MRSA accounted for more than 80 percent of *S. aureus* isolates in all reporting countries except Bolivia. The proportion of MRSA ranged from 47 percent in Bolivia to 100 percent in Chile and the Dominican Republic (PAHO, forthcoming).

Extended-spectrum beta-lactamase producers

Extended-spectrum beta-lactamases (ESBLs) are a family of enzymes, produced by Gram-negative bacteria, that confer resistance to some of the world's most widely prescribed antibiotics (WHO 2014; Reuland et al. 2014). ESBLs can inactivate all penicillins and cephalosporins, including third-

generation cephalosporins (e.g., ceftriaxone, cefotaxime, and ceftazidime) and monobactams (aztreonam).

In Europe, 17 of 22 countries reported that 85 to 100 percent of *E. coli* isolates were ESBL positive, and for *K. pneumoniae*, 13 of 21 countries reported ESBL percentages in the same range (EARS-Net 2014). In the United States, healthcare-associated ESBL-producing Enterobacteriaceae made up 14 percent of *E. coli* isolates and 23 percent of *K. pneumoniae* isolates (CDC 2013). In Canada, 7 percent of *E. coli* and 4 percent of *K. pneumoniae* isolates were ESBL producers (Denisuik et al. 2012). In New Zealand, ESBL-producing Enterobacteriaceae incidence increased from 10 people per 100,000 population in 2000 to 213 per 100,000 in 2013 (Heffernan and Woodhouse 2013). In Australia, 7 percent of *E. coli* and 5 percent of *K.*

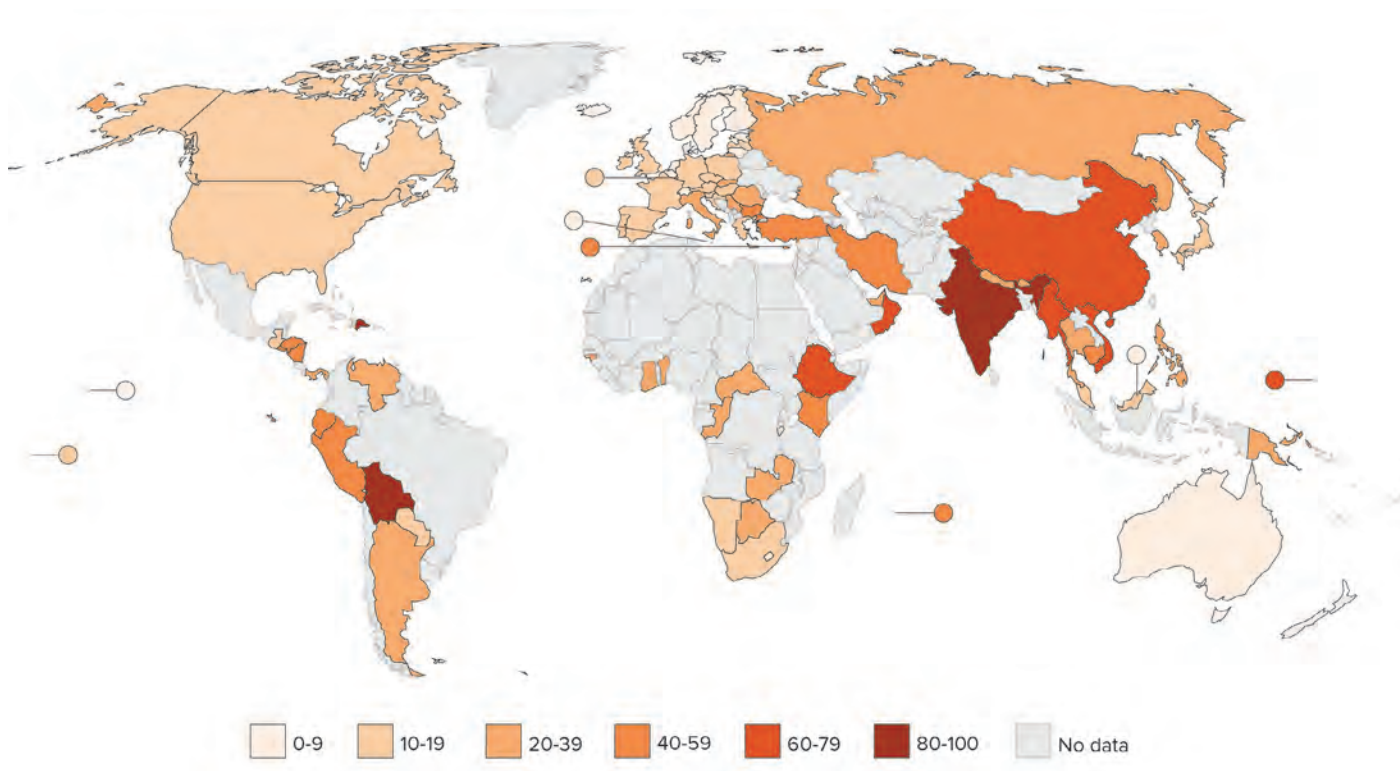


FIGURE 1-2: Percentage of extended-spectrum beta-lactamase producing *Escherichia coli, by country (most recent year, 2011–2014)**

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: Ceftriaxime, ceftriaxone and cefotaxime. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

*Indicated by third-generation cephalosporin resistance

pneumoniae isolates were found to be ESBL producers (Figure 1-2) (AGAR 2014).

ESBL-producing Enterobacteriaceae are of concern throughout Asia and are on the rise. In 2009 and 2010, 28 percent of all Enterobacteriaceae from urinary tract infections in 11 countries were ESBL producers, and resistance to third- and fourth-generation cephalosporins ranged from 26 to 50 percent in those countries (Lu et al. 2012). ESBL-producing *E. coli* increased from 40 to 61 percent between 2002 and 2009 in one hospital in New Delhi (Datta et al. 2012). In China, in 2011, ESBL-producing *E. coli* accounted for 71 percent of *E. coli* isolates, and more than half of *K. pneumoniae* strains produced ESBL (MOHNARIN 2011).

In Latin America, ESBL-producing Enterobacteriaceae prevalence is also rising. Rates of ESBL in *E. coli* were as high as 41 percent in 2009 in Mexico. In 2014, resistance of *K. pneumoniae* isolates to third-generation cephalosporins—a marker of ESBL production—ranged from 19 percent in Peru to 87 percent in Bolivia (PAHO, forthcoming).

In sub-Saharan Africa, the median prevalence of resistance to third-generation cephalosporins ranged from 0 to 47 percent (Leopold et al. 2014). In North Africa, ESBL prevalence ranged from 12 to 99 percent in hospitals and 1 to 11 percent in communities (Storberg 2014). In East Africa,

In 2014 [in Latin America], resistance of *K. pneumoniae* isolates to third-generation cephalosporins—a marker of ESBL production—ranged from 19 percent in Peru to 87 percent in Bolivia.

ESBLs were found in 38 to 63 percent of hospital samples and 6 percent of community samples (Storberg 2014). In Central Africa, 55 to 83 percent of hospital samples and 11 to 17 percent of community samples were ESBL positive (Storberg 2014). In West Africa, ESBLs were detected in 10 to 40 percent of hospital samples and 10 to 96 percent of community samples (Storberg 2014). And in South Africa, ESBL prevalence was 9 to 13 percent in hospitals and 0.3 to 5 percent in communities (Storberg 2014).

Carbapenem-resistant Enterobacteriaceae

Carbapenems are considered last-resort antibiotics, used for infections that are resistant to first-, second- and even third-line antibiotics. Infections with carbapenem-resistant Enterobacteriaceae (CRE) are increasingly reported from healthcare facilities, primarily in developed countries (Lerner

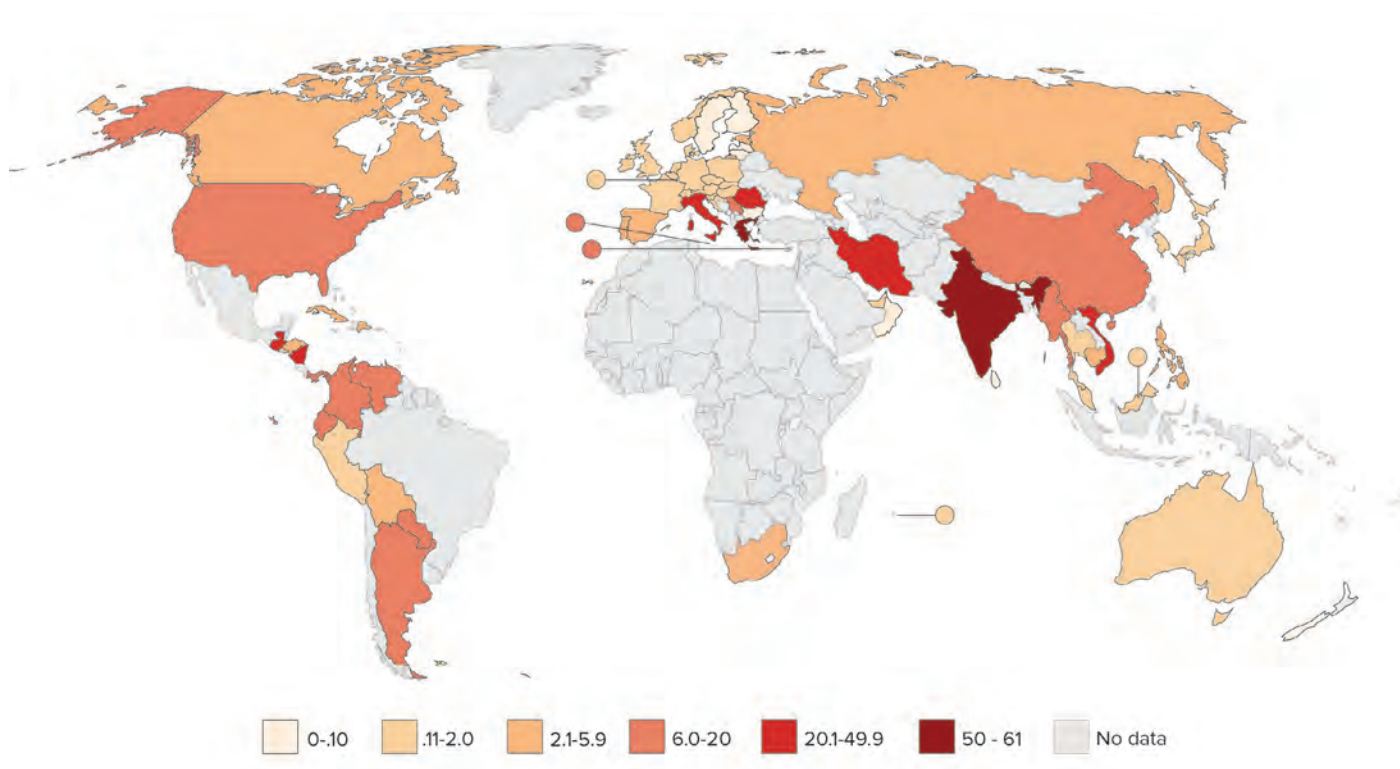


FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: imipenem, meropenem, ertapenem and doripenem. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

et al. 2014), but are also increasing in low- and middle-income countries.

In Canada, rates of CRE have remained stable (Public Health Agency of Canada 2015b). In the EU–European Economic Area,² carbapenem resistance was under 10 percent for *K. pneumoniae* and remained under 1 percent for *E. coli*, but five member countries reported increases in 2013, of which four were among the countries with the highest levels of resistance in the region (EARS-Net 2014). In the United States, 11 percent of *Klebsiella* spp. and 2 percent of *E. coli* isolates were resistant to carbapenems in 2012 (Figure 1-3) (CDC 2013).

In general, carbapenem resistance in Latin America is low. In 2013, resistance of *K. pneumoniae* to carbapenems ranged from full susceptibility of isolates to imipenem in the Dominican Republic to a high of 28 percent of isolates resistant to meropenem in Guatemala (PAHO, forthcoming).

In India, 10 percent of *E. coli* isolates were resistant to carbapenems in 2008, increasing to 13 percent in 2013. For *K. pneumoniae*, 29 percent were resistant in 2008, increasing to 57 percent in 2014 (CDDEP 2015b). Carbapenem resistance among *K. pneumoniae* increased from 2 percent in 2002 to 52 percent in 2009 in one tertiary-care hospital in New Delhi (Datta et al. 2012).

New Delhi metallo-beta-lactamase 1

New Delhi metallo-beta-lactamase 1 (NDM-1) is a genetic element with multiple resistance genes that can be harbored by and transmitted between Gram-negative bacteria, originally identified in a Swedish patient returning from New Delhi, India, in 2008. NDM-1 is highly resistant to most antibiotics except polymyxins (Moellering 2010). *E. coli* and *Klebsiella* spp. carrying NDM-1 now account for the majority of carbapenem resistance in some countries (Pillai et al. 2011). From their original detection in 2008, NDM-1–carrying Enterobacteriaceae have been identified in more than 70 countries in all regions (Figure 1-4) (Johnson and Woodford 2013). Initially, much of the global spread was attributed to travelers exposed through medical treatment or hospital stays in the Indian subcontinent and potentially the Balkans, but now, NDM-1–carrying organisms are being increasingly detected worldwide in cases unrelated to travel, suggesting local transmission. NDM-1 has also been identified in environmental samples from water sources in India and Vietnam, indicating that the gene is present in both community and hospital settings (Johnson and Woodford 2013).

Antibiotic-resistant *Neisseria gonorrhoeae*

Gonorrhea is a sexually transmitted infection, mainly of the reproductive tract, caused by the bacterium *N. gonorrhoeae*.

² EU–EEA population-weighted mean resistance based on countries that provided data.

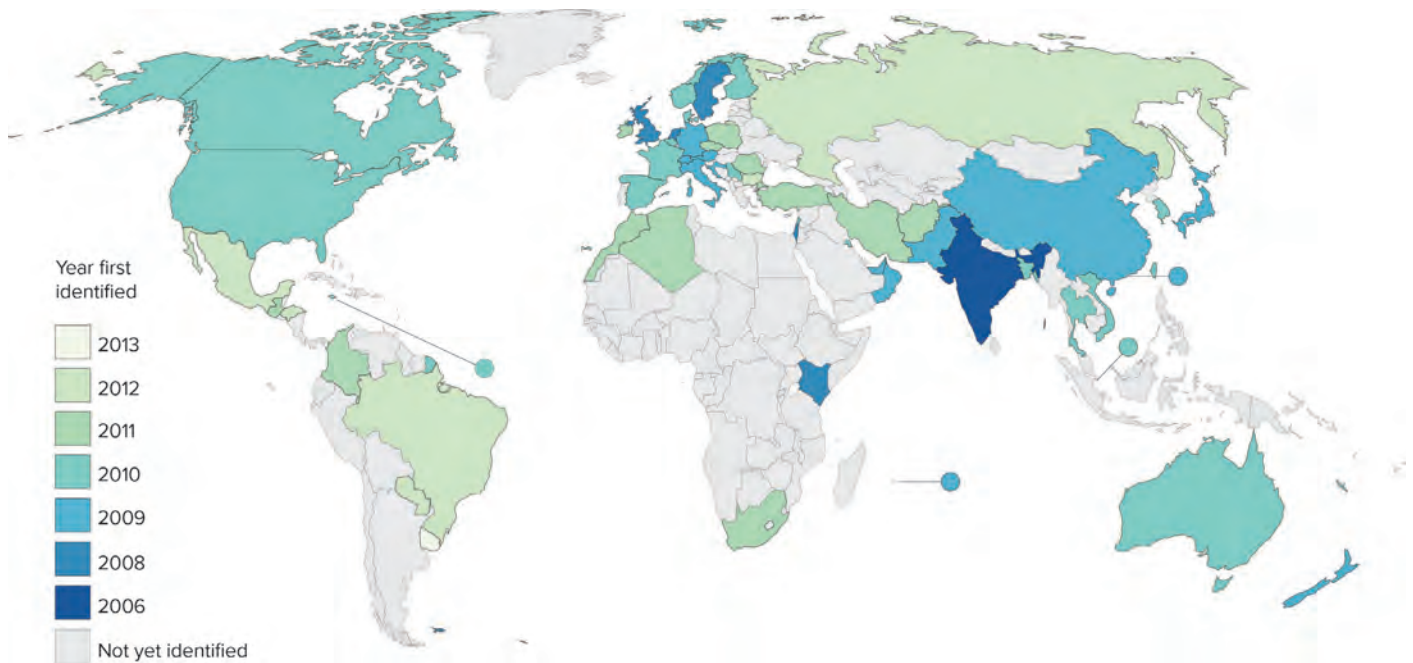


FIGURE 1-4: Spread of New Delhi metallo-beta-lactamase-1: first detection

Source: Johnson and Woodford 2013 (adapted)

In 2008, 106 million new cases of gonorrhoea occurred worldwide in 15- to 49-year-olds (WHO 2012). *N. gonorrhoeae* has developed resistance to several former first-line antibiotics, including sulfonamides, penicillins, tetracyclines, and fluoroquinolones. Currently, treatments of choice are third-generation cephalosporins (parenteral ceftriaxone and oral cefixime), the last remaining option for single-drug treatment. Susceptibility to third-generation cephalosporins has been declining in several parts of the world, and treatment failures in several countries have been reported.

In Europe in 2012, a lower proportion of isolates (4 percent) showed decreased susceptibility to cefixime compared with 2011 (ECDC 2012). In the United States, decreasing susceptibility to cefixime prompted the Centers for Disease Control and Prevention (CDC) to change treatment guidelines to dual therapy in 2012 (Kirkcaldy et al. 2013). In Canada, resistance has been on the rise, and 4 percent of isolates showed decreased susceptibility to a cephalosporin in 2013 (Public Health Agency of Canada 2015a). In Asia, susceptibility to third-generation cephalosporins is declining, and treatment failures were reported from Hong Kong, Japan, and Sri Lanka (WHO Western Pacific Region 2009). In Latin America, reduced susceptibility to ceftriaxone was first reported between 2007 and 2011 (Dillon et al. 2013). In Uganda, Tanzania, and Ghana, levels of resistance were high to ciprofloxacin but not to ceftriaxone (GARP–Tanzania National Working Group 2015; Vandepitte et al. 2014; Duplessis et al. 2015).

Clostridium difficile

Antibiotic treatment destabilizes the balance of intestinal microflora by killing off large numbers of bacteria, allowing *C. difficile*, which is naturally resistant to most antibiotics, to proliferate. *C. difficile* can be thought of as a serious adverse event related to antibiotic use, whether appropriate

***N. gonorrhoeae* has developed resistance to several former first-line antibiotics, including sulfonamides, penicillins, tetracyclines, and fluoroquinolones.**

or inappropriate (CDC 2013; McDonald et al. 2012). The infection can be lethal, especially to elderly people and those with impaired immune systems or other serious comorbidities (Fridkin et al. 2014), and is responsible for more than 14,000 deaths and 250,000 infections per year in the United States (CDC 2013). Although hospitals are the source of most *C. difficile* infections, those infections may originate in nursing homes and other outpatient settings (Lessa et al. 2015; McDonald et al. 2012). *C. difficile* is a global problem (Box 1-2).

Antibiotic use increases the risk of *C. difficile* infections by seven- to 10-fold for up to one month after discontinuation (Brown et al. 2015; Hensgens et al. 2012). *C. difficile* can be treated with antibiotics and is not significantly resistant to the available drugs.

Antibiotic stewardship programs and increased infection control measures have proven effective in reducing *C. difficile* infections in hospitals (Abbett et al. 2009; Feazel et al. 2014; Wenisch et al. 2014; Aldeyab et al. 2012; Talpaert et al. 2011). A 30 percent reduction in the use of broad-spectrum antibiotics in hospitalized patients could reduce the incidence of *C. difficile* infection by 26 percent (Fridkin et al. 2014).

Other emerging pathogens

Vancomycin-resistant enterococci (VRE) are another high-priority nosocomial pathogen whose presence has grown enormously over the past few years. The first isolates were discovered in 1987

BOX 1-2. CLOSTRIDIUM DIFFICILE AROUND THE WORLD

Africa

- In South Africa, the annual incidence of *C. difficile* infection was 8.7 cases per 10,000 admissions in a tertiary-care hospital. One-third of cases were community-acquired infections (Rajabally et al. 2013).
- In HIV patients in Nigeria, the prevalence of *C. difficile* infection was 43 percent among inpatients and 14 percent among outpatients who had diarrhea (Onwueme et al. 2011).

Asia

- *C. difficile* incidence ranged from 6.64 per 10,000 admissions in Singapore to 17.1 per 10,000 admissions in China (Collins et al. 2013).
- In 17 hospitals in South Korea, the incidence of *C. difficile* infections increased from 1.7 per 10,000 admissions in 2004 to 2.7 per 10,000 admissions in 2008 (Kim et al. 2013).

Australia

- In 450 public hospitals across Australia, the incidence of *C. difficile* infection increased from 3.25 per 10,000 patient-days in 2011 to 4.03 per 10,000 patient-days in 2012 (Slimings et al. 2014).
- One-quarter of the infections came from community settings (Slimings et al. 2014).

Europe

- In 106 laboratories across 34 countries, the incidence of *C. difficile* infection was 4.1 per 10,000 patient-days (range 0.0–36.3) (Bauer et al. 2011).
- Based on *C. difficile* testing in 482 hospitals across 20 countries, an estimated 40,000 inpatients in these hospitals have undiagnosed *C. difficile* infections every year (Davies et al. 2014).

Latin America and the Caribbean

- *C. difficile* infection incidence ranged from 12.9 per 10,000 admissions in Peru to 42 per 10,000 admissions in Argentina (Balassiano et al. 2012).

North America

- *C. difficile* causes 250,000 cases and 14,000 deaths annually in the United States (CDC 2013).
- In 29 hospitals throughout Canada, the *C. difficile* infection incidence rate was 4.6 cases per 10,000 admissions and 65 per 100,000 patient-days. The attributable mortality rate was 5.7 percent (Gravel et al. 2009).

A 30 percent reduction in the use of broad-spectrum antibiotics in hospitalized patients could reduce the incidence of *C. difficile* infection by 26 percent.

in Europe, and within a decade they made up more than 25 percent of *Enterococcus* bloodstream infections in hospitals in the United States (Willems et al. 2005). By 2013, 77 percent of *E. faecium* healthcare-associated infections in the United States were resistant to vancomycin (CDC 2013).

Multidrug resistance has also been increasingly detected in *Salmonella* Typhi isolates, responsible for typhoid fever. Genetic sequencing revealed that a particularly resistant strain, H58, originated in Asia and Africa and has spread throughout these regions for 30 years in epidemic fashion (Wong et al. 2015). This strain has the potential to spread very rapidly: it was first detected in Malawi in 2011, and by 2014 multidrug-resistant prevalence there had increased to 97 percent, from 7 percent prior to 2010 (Feasey et al. 2015).

RESISTANCE RATES AND TRENDS

Antibiotic resistance patterns of individual pathogens to the drugs used to treat them vary considerably between and within countries. These differences are driven by different patterns of antibiotic use, distinct national disease burdens, disparities in access to first- and second-line treatments, and the burden of coinfections, particularly malaria, the human immunodeficiency virus (HIV), and tuberculosis (O'Neill 2014).

Resistance rates have also been correlated with seasonal antibiotic use: in the United States, spikes of resistant *E. coli* correlated significantly with seasonal highs in aminopenicillin and fluoroquinolone prescriptions, lagging by one month (Sun et al. 2012).

Some antibiotic-resistant infections, such as *H. influenzae* in children under five, have higher mortality rates compared with susceptible infections (27 versus 7 percent mortality) (Roca et al. 2008). However, this increased risk of death is not universal: in the case of healthcare-associated infections, antibiotic resistance does not greatly increase mortality or length of hospital stay due to bloodstream infections (risk of death 1.2, CI 0.9 to 1.5) or pneumonia (risk of death 1.2, CI 1.1 to 1.4) (Lambert et al. 2011).

Antibiotic-resistant infections also contribute to the financial burden on healthcare systems. In Europe, they cost an estimated €1.5 billion annually, including healthcare expenditures and productivity losses (i.e., both direct and indirect costs) (EMA and ECDC 2009). In the United States, the annual cost to the healthcare system is as much as \$20 billion, and productivity losses total another \$35 billion (CDC 2013).

High-income regions and countries

In the United States, CDC (2013) has estimated that more than 2 million infections and 23,000 deaths are due to antibiotic resistance each year. In Europe, an estimated

25,000 deaths are attributable to antibiotic-resistant infections (EMA and ECDC 2009).

Resistance of *Streptococcus pneumoniae* invasive isolates to antibiotics has declined in the United States, from 34 to 17 percent from 1999 to 2013 for penicillins, and from 15 to 8 percent from 1999 to 2012 for third-generation cephalosporins. From 1999 to 2012, resistance to macrolides increased from 23 to 34 percent, but fluoroquinolone resistance remained stable, at 2 percent. Among *E. coli* and *K. pneumoniae* isolates, resistance to third-generation cephalosporins and fluoroquinolones increased steadily: for third-generation cephalosporin resistance in *E. coli*, from 2 to 12 percent, and in *K. pneumoniae*, from 8 to 19 percent; for fluoroquinolone resistance in *E. coli*, from 5 to 30 percent, and in *K. pneumoniae*, from 7 to 18 percent. Among *E. faecium* invasive isolates, vancomycin resistance increased from 65 to 76 percent. Compared with other high-income countries, the United States has higher rates of resistance to many Gram-positive bacteria, including VRE and MRSA (CDDEP 2015a).

In 2013, EARS-Net reported that overall resistance rates for many drug-bug combinations were higher in Southern and Eastern Europe than in the rest of Europe. Resistance rates of Gram-negative bacteria were high, and for nearly all the pathogens under surveillance, resistance to at least one antimicrobial group was observed. Multiple-drug resistance among Gram-negative bacteria to third-generation cephalosporins, fluoroquinolones, and aminoglycosides was common (EARS-Net 2014).

EARS-Net also reported that in 2013, among *S. pneumoniae* invasive isolates, penicillin resistance was highest in Poland (32 percent) and lowest in the Netherlands (1 percent), and for macrolides, resistance was highest in Romania (38 percent) and lowest in Latvia (2 percent). Among *E. faecium* isolates in 2013, vancomycin resistance was highest in Ireland (43 percent) and lowest in Sweden and Estonia (0 percent). Among *E. coli* isolates, third-generation cephalosporin resistance was highest in Bulgaria (41 percent) and lowest in Iceland (5 percent), and for fluoroquinolones, resistance was highest in Cyprus (52 percent) and lowest in Norway (12 percent). Similarly, among *K. pneumoniae* invasive isolates, third-generation cephalosporin resistance was highest in Bulgaria (71 percent) and lowest in Iceland (0 percent), and for fluoroquinolones, resistance was highest in Poland (72 percent) and lowest in Finland (5 percent). Carbapenem resistance was more common in *K. pneumoniae* than in *E. coli*. Carbapenem resistance among *K. pneumoniae* invasive isolates was highest in Greece (60 percent). In 2013, carbapenem resistance in *K. pneumoniae* was not detected in Bulgaria, Finland, Latvia, Lithuania, or Sweden (EARS-Net 2014).

In Canada, as in several other countries, *S. pneumoniae* resistance has decreased following the introduction of pneumococcal vaccines (Public Health Agency of Canada 2015b; Callaway 2014). Among *S. pneumoniae* invasive isolates in 2012, penicillin resistance was 8 percent, and macrolide resistance was 23 percent. Among *E.*

In Canada, as in several other countries, *S. pneumoniae* resistance has decreased following the introduction of pneumococcal vaccines.

coli isolates, third-generation cephalosporin resistance was 10 percent, and fluoroquinolone resistance was 27 percent. Similarly, among *K. pneumoniae* invasive isolates, resistance to third-generation cephalosporins was 8 percent, compared with 3 percent resistance to fluoroquinolones. In 2012, carbapenem resistance was not detected in *E. coli*, but 2 percent of *K. pneumoniae* isolates were carbapenem resistant (CANWARD 2013).

In Australia in 2013, 41 percent of *E. faecium* bloodstream isolates were vancomycin resistant. Among *E. coli* isolates, 10 percent were fluoroquinolone resistant and 8 percent were third-generation cephalosporin resistant. Among *K. pneumoniae* isolates, 5 percent were fluoroquinolone resistant and 6 percent were third-generation cephalosporin resistant. Carbapenem resistance was observed in less than 1 percent of *K. pneumoniae* and *E. coli* isolates (AGAR 2013a, 2013b).

In New Zealand from 2009 to 2012, the prevalence of penicillin-resistant *S. pneumoniae* was fairly consistent (ESR 2013b). In 2012, 17 percent of *S. pneumoniae* isolates were penicillin resistant. Vancomycin resistance among *Enterococcus* spp. increased from 0.3 percent in 2002 to 2 percent in 2013. Among *E. coli* isolates, fluoroquinolone resistance increased from 2 percent to 12 percent in the same period, and third-generation cephalosporin resistance increased from 3 percent to 9 percent. In 2013, carbapenem resistance was observed in 0.3 percent of *E. coli* invasive isolates, but no resistance was observed in *Klebsiella* spp. (ESR 2002, 2013a).

Low- and middle-income regions and countries

K. pneumoniae is the most commonly reported Gram-negative pathogen in Asia and Africa, making up nearly half of all Gram-negative infections in neonates. In Asia, median resistance of *K. pneumoniae* to ampicillin was 94 percent, and to cephalosporins, 84 percent; in Africa, it was 100 and 50 percent, respectively. Multidrug resistance appeared in 30 percent of strains in Asia and 75 percent of strains in Africa (Le Doare et al. 2014).

In sub-Saharan Africa, rates of multidrug resistance exceeding 50 percent have been reported in invasive typhoidal and nontyphoidal *Salmonella* infections. Resistance to the drugs used to treat multidrug-resistant *Salmonella*, such as fluoroquinolones, is also increasing (Kariuki et al. 2015). Invasive nontyphoidal *Salmonella* infections are responsible for more than 600,000 deaths per year, 55 percent of them in Africa (Kariuki et al. 2015).

Patterns of antibiotic resistance differ slightly in Latin America and the Caribbean, where prevalence of community-associated Enterobacteriaceae infections is

higher than in the rest of the world, especially in urinary tract infections caused by *E. coli* and intra-abdominal infections caused by *E. coli* and *Klebsiella* spp. These infections show increasing resistance to trimethoprim-sulfamethoxazole, quinolones, and second-generation cephalosporins. In 2009, rates of resistance in urinary tract *E. coli* isolates reached 71 percent in women and 85 percent in men, with the highest rates occurring in Argentina and Peru (Salles et al. 2013).

In Latin America and the Caribbean in 2013, resistance in community *S. pneumoniae* isolates was generally low to penicillins but ranged from 0 percent in Bolivia to 97 percent in Chile. No resistance was detected to vancomycin, and very low resistance was detected in some countries to third-generation cephalosporins. Resistance in *E. faecium* hospital isolates was higher than for *E. faecalis*. Resistance in *E. faecium* was high to ampicillins and vancomycin, reaching 100 percent resistance to ampicillins in Ecuador, El Salvador, and Paraguay. Paraguay also had the highest resistance to vancomycin, at 75 percent. *E. faecalis* resistance to ampicillin ranged from 0 to 15 percent, and resistance to vancomycin ranged from 0 to 22 percent (PAHO, forthcoming).

In Nepal, resistance rates exceeded 50 percent for *S. pneumoniae* and *K. pneumoniae* isolates to commonly used treatments, having increased from 2000 to 2008. Resistance of *Salmonella* Typhi and *Salmonella* Paratyphi strains have also increased since 1998 to the present, and in *E. coli*, from 2006 to 2010. Resistance rates were above 50 percent to all drugs tested in *E. coli* urinary tract infections, and high resistance rates were detected in gonorrheal infections (GARP–Nepal National Working Group 2014).

In India, *E. coli* resistance in pregnant women and schoolchildren to at least one antibiotic exceeded 40 and 60 percent, respectively. High levels of resistance were detected in *N. gonorrhoeae* isolates: although all were sensitive to ceftriaxone, nearly a fourth were beta-lactamase producers. Resistance in *K. pneumoniae* to second-, third-, and fourth-generation cephalosporins was in the 25 to 55 range in 2004–2005 (GARP–India National Working Group 2011).

Resistance to fluoroquinolones among invasive *Salmonella* Typhi isolates in India increased from 8 percent in 2008 to 28 percent in 2014. However, resistance in 2014 to two older antibiotics—ampicillin, 5 percent, and cotrimoxazole, 4 percent—is decreasing and much lower than rates of resistance to fluoroquinolones. From 2008 to 2013, *E. coli* resistance to third-generation cephalosporins increased from 70 to 83 percent, and fluoroquinolone resistance increased from 78 to 85 percent. Among *K. pneumoniae* isolates, third-generation cephalosporin resistance decreased from 90 to 80 percent, and fluoroquinolone resistance increased from 57 to 73 percent. In 2014, carbapenem resistance was 57 and 12 percent among *K. pneumoniae* and *E. coli* isolates, respectively. Among *E. faecium* isolates, 11 percent were vancomycin resistant (CDDEP 2015b).

In China, more than 90 percent of *E. faecium* isolates were ampicillin resistant. Among nonmeningitis *S. pneumoniae* isolates, 15 percent were penicillin resistant. Seventy-one percent of *E. coli* isolates and more than half of *K. pneumoniae* isolates were ESBL producers (MOHNARIN 2011).

In Vietnam, among *E. coli* isolates, resistance to third-generation cephalosporins was 64 percent, and to fluoroquinolones, 50 percent. Among *K. pneumoniae* isolates, resistance to third-generation cephalosporins was 42 percent, and to fluoroquinolones, 22 percent. Carbapenem resistance was reported in 9 percent of *E. coli* isolates and 22 percent of *K. pneumoniae* isolates. Increasing levels of resistance to ceftriaxone, the primary treatment for bacterial meningitis, have been detected among cases of invasive pneumococcal disease since 2012 (CDDEP 2015b; personal communication, Heiman Wertheim).

Vietnam in 2000–2001 had the highest prevalence of *S. pneumoniae* resistance to penicillin and erythromycin of all countries participating in the Asian Network for Surveillance of Resistant Pathogens, at 71 and 92 percent, respectively (Kim et al. 2012). Penicillin resistance in *S. pneumoniae* increased from 8 to 56 percent from the 1990s through 2000. Resistance was also common to Gram-negative bacteria, including more than a quarter of isolates to third-generation cephalosporins in the same period. A more recent study reported ceftazidime resistance of 42 percent (GARP–Vietnam National Working Group 2010).

In Thailand, penicillin resistance among *S. pneumoniae* isolates decreased from 81 percent in 2009 to 39 percent in 2013. However, macrolide resistance increased from 30 percent in 2009 to 37 percent in 2014. From 2009 to 2013, vancomycin resistance among *E. faecium* isolates decreased from 3 to 1 percent. In the same period, among *E. coli* isolates, third-generation cephalosporin resistance increased from 29 to 37 percent, and fluoroquinolone resistance increased from 38 to 44 percent. Among *K. pneumoniae* isolates, third-generation cephalosporin resistance remained stable, at 32 percent. Fluoroquinolone resistance increased from 28 to 30 percent. In 2013, carbapenem resistance was 2 percent and 0.8 percent among *K. pneumoniae* and *E. coli* isolates, respectively (NARST 2013).

Very limited data are available on resistance rates in sub-Saharan Africa. What studies have been done reported that, among isolates of Enterobacteriaceae in patients with febrile illness, 31 to 94 percent were resistant to chloramphenicol and 0 to 47 percent to third-generation cephalosporins. Among isolates of *Salmonella* Typhi, 15 to 43 percent were resistant to nalidixic acid. Though even fewer studies are available on Gram-positive pathogens and urinary tract, meningitis, respiratory tract, and hospital-acquired infections, there, too, high rates of resistance to first-line treatments have been reported (Leopold et al. 2014).

Kenya experienced a rise in resistance of *S. pneumoniae* isolates to penicillin from 25 percent in the 1980s to 43 percent in 2003. Half of children's severe pneumonia infections were resistant to penicillin in 2005. More than two-thirds of *H. influenzae* b were resistant to cotrimoxazole

in 2002. Resistance was also high in diarrheal pathogens: three-quarters were resistant to three or more drugs in 2001. Resistance increased in nontyphi *Salmonella* from the 1990s to 2005, and the prevalence of multidrug resistance exceeded 40 percent in 2003. Multidrug-resistant *Salmonella* Typhi also increased, to 78 percent in 2004 (GARP–Kenya National Working Group 2011).

A private tertiary hospital in Kenya reported that, among *E. coli* isolates, third-generation cephalosporin resistance was 53 percent and fluoroquinolone resistance was 59 percent. Among *K. pneumoniae* isolates, third-generation cephalosporin resistance was 67 percent and fluoroquinolone resistance was 30 percent. In 2012 in this hospital, carbapenem resistance was not detected in *E. coli* or *K. pneumoniae* isolates, and methicillin and vancomycin resistance was not detected among *S. aureus* and *Enterococcus* isolates, respectively. In 2013, carbapenem resistance emerged among *Klebsiella* spp., but not among *E. coli* isolates (personal communication, Revathi Gunturu).

South Africa detected a high prevalence of intermediate resistance in *S. pneumoniae* isolates to penicillin, and resistance of *H. influenzae* isolates to penicillin was more than 45 percent in some settings. Resistance declined among nontyphoidal *Salmonella* isolates from 2003 to 2010. Resistance in *Shigella* isolates was stable from 2003 to 2010 in older antibiotics, at more than 50 percent, and it was at or below 1 percent for newer antibiotics. Less than 1 percent of diarrheagenic *E. coli* isolates were resistant to the drugs tested. Gonococci were fully susceptible to ciprofloxacin, a former first-line therapy, which was replaced with cephalosporins after a rise in quinolone resistance in the early 2000s (GARP–South Africa National Working Group 2011).

Laboratory surveillance data in South Africa show that from 2012 to 2014, vancomycin resistance among *E. faecium* isolates decreased from 25 to 7 percent. Among *E. coli* isolates, third-generation cephalosporin resistance remained stable, at 19 percent, and fluoroquinolone resistance also remained stable, at 28 percent. Among *K. pneumoniae* isolates, third-generation cephalosporin resistance remained stable, at 32 percent, but fluoroquinolone resistance increased slightly, from 28 to 30 percent. In 2013, carbapenem resistance was 2 and 0.8 percent among *K. pneumoniae* and *E. coli* isolates, respectively (CDDEO 2015b).

In Mozambique, nearly 90 percent of *S. pneumoniae* isolates were resistant to cotrimoxazole, and resistance to first-line treatments increased significantly for *H. influenzae*, approaching 50 percent for both (GARP–Mozambique National Working Group 2015). Uganda reported high levels of resistance in *S. pneumoniae* to first-line treatments. High rates of resistance were also reported in *Shigella* isolates to several drugs, but there was low resistance to quinolones. In bacteria causing sepsis, 60 to 100 percent of isolates were resistant to most antibiotics tested, though resistance was less than 5 percent to newer antibiotics (GARP–Uganda, in press). Tanzania found high levels of resistance in *S. pneumoniae* in children, as well as in

bacterial diarrheal infections, and detected increased mortality due to resistant neonatal sepsis cases. Increasing rates of resistance were found in urinary tract and sexually transmitted infections, particularly gonorrhea and syphilis (GARP–Tanzania 2015).

SURVEILLANCE SYSTEMS

Many countries have at least partial surveillance systems in place to report and track antibiotic resistance trends.

National surveillance

AUSTRALIA

Several organizations collect resistance data, including the Centre for Healthcare Related Infection Surveillance and Prevention, the Healthcare Infection Surveillance of Western Australia, the Tasmanian Infection Prevention and Control Unit, and the Victorian Nosocomial Infection Surveillance System, in addition to pathology laboratories participating in the SENTRY program and the Australian Group on Antimicrobial Resistance (AGAR). AGAR was started in 1985 and surveys organisms from hospital and community sources, monitoring trends over time.

CANADA

The Canadian Antimicrobial Resistance Surveillance System was established in 2015 and will consolidate surveillance from seven existing systems. Data on resistance in community- and hospital-associated infections have also been collected by the Canadian Antibiotic Resistance Alliance (CARA) since 2007.

CHINA

The Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN) conducts surveillance. In 2011, microbiology laboratories in 49 tertiary-care centers contributed antimicrobial susceptibility information.

INDIA

The Indian Council of Medical Research began setting up the Anti-Microbial Resistance Surveillance Network in 2011. When complete, its seven nodes will focus on (i) diarrhea (e.g., *Shigella*, *Vibrio cholerae*), (ii) enteric fever (e.g., *Salmonella* Typhi, *S. Paratyphi*), (iii) sepsis caused by Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella pneumoniae*), (iv) other Gram-negative organisms (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*), (v) Gram-positive bacteria (e.g., MRSA and VRE), (vi) fungal infections (e.g., *Candida* spp.), and (vii) respiratory pathogens (e.g., *Streptococcus pneumoniae*). Each node will focus on certain set of organisms. Medical colleges across the country will act as regional centers.

Antibiotic resistance data in India are also collected as a part of CDDEP's ResistanceMap (www.resistancemap.org), which represents invasive isolates from blood and cerebrospinal fluid. ResistanceMap tracks the following pathogens: *E. coli*, *K. pneumoniae*, *A. baumannii*, *S. aureus*, *P. aeruginosa*, *Enterobacter* spp., *Salmonella* Typhi, *Salmonella* Paratyphi, and *Enterococcus* spp. (Box 1-3).

India is represented by data from SRL, a large private laboratory network from 2008 to 2014. This network includes 5,700 collection centers in 26 of India's 29 states and two of seven Union Territories. The collection centers include private hospitals (tertiary care, secondary care) and diagnostic laboratories; samples are also collected in patients' home. Efforts are underway to expand the ResistanceMap network to include other large private laboratories and both private and public hospitals in India.

NEW ZEALAND

The Public Health Surveillance Program collects and analyzes antimicrobial resistance data generated from routine diagnostic susceptibility testing in hospital and community microbiology laboratories. About 30 laboratories currently contribute data on a wide range of organisms and antimicrobials.

PHILIPPINES

The Antimicrobial Resistance Surveillance Program of the Department of Health was established in 1988. It collects data from 22 sentinel sites and three gonococcal surveillance sites. The reference laboratory at the Research Institute for Tropical Medicine compiles and analyzes the data.

SOUTH AFRICA

South Africa currently collects reliable data from both public and private sectors using laboratory-based surveillance for the ESKAPE organisms (*Enterococcus*, *S. aureus*, *Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas* spp., and ESBL-producing *Enterobacteriaceae*). In the public sector, the laboratory data are reported by the National Institute for Communicable Diseases and include data collected from public sentinel hospitals by the Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA), a national clinical microbiology network. Surveillance on 12 pathogens is conducted in 31 hospitals and more than 200 laboratories. In addition, data are collected from the private sector by the South African Society of Clinical Microbiology, which collates private laboratory data from five laboratory groups for 13 pathogens. These data do not cover the entire population and are not necessarily nationally representative. The two data sets are now being consolidated through the South African Antibiotic Resistance Partnership and GARP.

THAILAND

Data on antibiotic resistance are collected by the National Institute of Health's National Antimicrobial Resistance Surveillance Thailand (NARST) program. NARST was founded in 1998 and collects data from 33 hospitals.

UNITED STATES

Surveillance is conducted by CDC's Active Bacterial Core surveillance (ABCs) program on selected pathogens that cause infections mainly in the community setting. ABCs has been collecting data since 1995, currently in sites in 10 states, covering a total population of more than 42 million for most pathogens. Case finding is active and laboratory based and includes results from hospitals and reference laboratories. In July 2014, the CDC National Health Safety

Network program began antimicrobial resistance surveillance and will collect antimicrobial resistance information on 19 organisms. Previously, surveillance data on some 500 taxa and 119 antimicrobial agents had been collected by a commercial system, The Surveillance Network (TSN, Eurofins-Medinet, Chantilly, Virginia), from more than 300 healthcare institutions.

VIETNAM

Data on antibiotic resistance are collected by the VINARES project (Viet Nam Resistance Project) from 16 hospitals in different regions of the country. VINARES was started in 2012 and is coordinated by researchers from Oxford University Clinical Research Unit in Hanoi and Linköping University, Sweden.

Regional surveillance

ASIA

The Asian Network for Surveillance of Resistant Pathogens, begun in 1996, is the first collaborative multicountry research group in Asia focused on antibiotic resistance. Initiated to investigate pneumococcal resistance, the group has expanded to study other bacterial pathogens. Since 2010, it has collected data from more than 120 centers in 14 countries in Asia and the Middle East.

CENTRAL ASIA AND EASTERN EUROPE

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance network is a joint initiative of the European Society of Clinical Microbiology and Infectious Diseases, the Dutch National Institute for Public Health and the Environment, and WHO/Europe. It aims to initiate national antimicrobial resistance surveillance systems in countries of this region that are not currently included in EARS-Net (see next subsection).

BOX 1-3. RESISTANCEMAP: A TOOL FOR VISUALIZING ANTIBIOTIC RESISTANCE

ResistanceMap (www.resistancemap.org) is a tool developed by CDDEP that allows users to view the evolution of national and regional resistance rates of each pathogen to classes of antibiotics or specific antibiotics in the United States from 1999 to 2012. Where comparable data are available, rates are also provided for Australia, Canada, Europe, India, Kenya, New Zealand, South Africa, Thailand, and Vietnam. ResistanceMap can also be used to visualize outpatient antibiotic use (by class and by U.S. state from 1999 to 2012) and global trends in antibiotic use (by class and country from 2000 to 2010).

CDDEP is expanding ResistanceMap to include additional data from low- and middle-income countries. The Pan American Health Organization and the Global Antibiotic Resistance Partnership, among other partners, are working to identify data sources and enable collaboration.

EUROPE

The European Antimicrobial Resistance Surveillance Network (EARS-Net) has tracked antimicrobial resistance on selected pathogens since 1999. EARS-Net is a network of some 900 microbiological laboratories serving more than 1,500 hospitals in 30 countries. Tests results come from clinical laboratories in each country, and pathogens are isolated from blood and cerebrospinal fluid only.

LATIN AMERICA AND THE CARIBBEAN

Resistance data for this region have been collected since 1996 by the Latin American Antibiotic Resistance Surveillance network (Red Latinoamericana de Vigilancia de la Resistencia a los Microbianos), coordinated by the Pan American Health Organization. Data are collected from 19 national reference laboratories, served by more than 750 sentinel sites, on 11 community and seven nosocomial pathogens.

CONCLUSIONS

Resistance among common pathogens causing community- and hospital-associated infections is increasing worldwide, though regional patterns of resistance vary. Significantly, resistance to last-resort antibiotics has led to an epidemic

Resistance to last-resort antibiotics has led to an epidemic of hard-to-treat infections, such as MRSA, ESBL-producing Enterobacteriaceae, CRE, NDM-1, VRE, and gonorrheal infections.

of hard-to-treat infections, such as MRSA, ESBL-producing Enterobacteriaceae, CRE, NDM-1, VRE, and gonorrheal infections. These infections have the potential to spread quickly through international trade and travel. *C. difficile*, an infection that can occur following antibiotic treatment, is another serious threat to human health related to antibiotic use.

Antibiotic resistance patterns follow patterns in antibiotic use: for newer antibiotics, lower resistance levels are reported, particularly in developing countries, where new drugs may be unaffordable for most.

Most low- and middle-income countries lack national surveillance systems, but some (e.g., India) are developing national networks. More comprehensive data collection and systematic examination and dissemination of existing data are needed to complete the global picture of antibiotic resistance.

2 HUMAN USE OF ANTIBIOTICS

KEY MESSAGES

- Antibiotic consumption in humans is increasing globally. The greatest increase between 2000 and 2010 was in low- and middle-income countries (LMICs), but in general, high-income countries still use more antibiotics per capita.
- An estimated 80 percent of all antibiotics are used in the community, where prescribing and purchasing of antibiotics without prescription are common, especially in LMICs. In many countries at all economic levels, clinicians have incentives to overuse antibiotics.
- The confluence of patients with serious medical conditions, interconnectedness of hospitals through mobile patient populations, and high density of antibiotic use make hospital antibiotic use disproportionately important.

Growing economic prosperity and rising incomes, as well as expanding insurance coverage, have increased antibiotic consumption (Filippini et al. 2006; Matuz et al. 2006; Harbarth and Monnet 2008). In the United States, antibiotic use among older adults increased after insurance coverage was expanded through Medicare Part D, particularly of broad-spectrum antibiotics (Zhang et al. 2010) (Box 2-1). Increased access to antibiotics has lowered morbidity and mortality and is also driving antibiotic resistance.

GLOBAL ANTIBIOTIC CONSUMPTION

New estimates of global antibiotic use that include LMICs have recently been published, combining direct sales data from manufacturers and indirect sales data from wholesalers to estimate the total volume of antibiotics sold in hospital and retail pharmacies for 71 countries from 2000 through 2010 (Van Boeckel et al. 2014 based on IMS MIDAS)¹.

Between 2000 and 2010, total global antibiotic consumption grew by more than 30 percent, from approximately 50 billion to 70 billion standard units² (SU). Penicillins and cephalosporins accounted for nearly 60 percent of total consumption in 2010 (Figure 2-1), increasing by 41 percent from 2000. Among the oldest antibiotics on the market, these are still the most common first-line antibiotics and the primary treatment for common infections around the world (Van Boeckel et al. 2014 based on IMS MIDAS).

Worldwide, increases were also significant for two “last-resort” antibiotic classes: carbapenems (approximately 40 percent) and polymyxins (13 percent) (Van Boeckel et al. 2014 based on IMS MIDAS). The growth in retail carbapenem sales was particularly steep in India, Pakistan, and Egypt (some drugs may have been prescribed in hospitals and filled at a pharmacy) (Figure 2-2).

Worldwide, increases were also significant for two “last-resort” antibiotic classes: carbapenems (approximately 40 percent) and polymyxins (13 percent).

Carbapenems are a class of beta-lactams chiefly employed against Gram-negative infections, which are among the most difficult to treat. Polymyxins are last-resort drugs used to treat multidrug-resistant infections, such as carbapenem-resistant Enterobacteriaceae (CRE). The largest within-class increases were in monobactams, with more than a 2,000-fold increase, and glycopeptides, whose use doubled (Van Boeckel et al. 2014 based on IMS MIDAS). Glycopeptides include vancomycin, which is often used when methicillin-resistant *Staphylococcus aureus* (MRSA) infection is confirmed or suspected.

Carbapenem use has also increased rapidly in Europe, with regional variations: in 1997 yearly per capita consumption in the hospital sector, measured in defined daily doses (DDD) per 1,000 inhabitants per day (DID), ranged from 0.0014 in Slovenia to 0.029 in Belgium. In 2013, the range was from 0.0136 DID in Bulgaria to 0.381 DID in the UK (ESAC-Net 2015) (Figure 2-3).

Top global consumers

The countries consuming the most antibiotics overall in 2010 were India, 13 billion SU; China, 10 billion SU; and the United States, 7 billion SU. However, in per capita terms among these countries, the United States led in 2010 with 22 SU per person, compared with 11 SU in India and 7 SU in China (Van Boeckel et al. 2014 based on IMS MIDAS).

¹ Original source of human antibiotic consumption data (Laxminarayan et al. 2013, Van Boeckel et al. 2014 (based on IMS MIDAS) and Laxminarayan 2014): IMS MIDAS International Prescription Data, January, 2000–December, 2010, IMS Health Incorporated. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

This report excludes values for Australia and New Zealand because of data reliability issues. All figures represent the remaining 69 countries.

² As defined by IMS, a standard unit is a measure of volume based broadly on the smallest identifiable dose given to a patient, dependent on the pharmaceutical form (a pill, capsule, or ampoule).

BOX 2-1. MEDICARE PART D

Medicare Part D, a prescription drug plan for Medicare subscribers in the United States, covers individuals aged 65 and over and some individuals under 65 receiving disability or diagnosed with specific diseases. In 2013, there were roughly 36 million Medicare Part D beneficiaries (68 percent of all Medicare subscribers) and almost 1.2 billion claims for drug prescriptions. Prescriptions for antibiotics among Medicare Part D recipients made up roughly 4 percent of all claims, totaling 42.9 million claims and more than \$1 billion in drug costs. The most common antibiotics prescribed to Medicare Part D beneficiaries were azithromycin, ciprofloxacin, and amoxicillin. The highest total antibiotic drug costs for recipients were for doxycycline (\$149.3 million), followed by rifaximin (\$130.4 million) and moxifloxacin (\$91.3 million).

Antibiotic prescriptions were most commonly given by family practice physicians (10.4 million claims), internal medicine practitioners (10.4 million claims), and dentists (3 million claims). Antibiotic prescribing was highest in California (4.1 million claims), Florida (3.5 million claims), and Texas (3.1 million claims).

10 MOST COMMON ANTIBIOTICS PRESCRIBED TO MEDICARE PART D BENEFICIARIES, 2013

Antibiotic	Total claims (in millions)	Total cost (in millions)
Azithromycin	6.3	\$ 83.1
Ciprofloxacin	5.8	\$ 41.5
Amoxicillin	4.5	\$ 24.8
Trimethoprim and sulfamethoxazole (cotrimoxazole)	3.5	\$ 23.9
Cephalexin	3.4	\$ 26.5
Levofloxacin	3.2	\$ 46.5
Amoxicillin and clavulanate	2.2	\$ 49.0
Doxycycline	2.0	\$149.3
Nitrofurantoin	1.5	\$ 68.9
Mupirocin	1.3	\$ 22.0

Source: Centers for Medicare & Medicaid Services (<http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html>).

The United States accounts for about 10 percent of the world's consumption. From 1999 to 2010, per capita outpatient antibiotic prescribing in the United States decreased by 15 percent, with 0.81 prescriptions per capita in 2010; however, this increased to 0.9 prescriptions per capita in 2012,

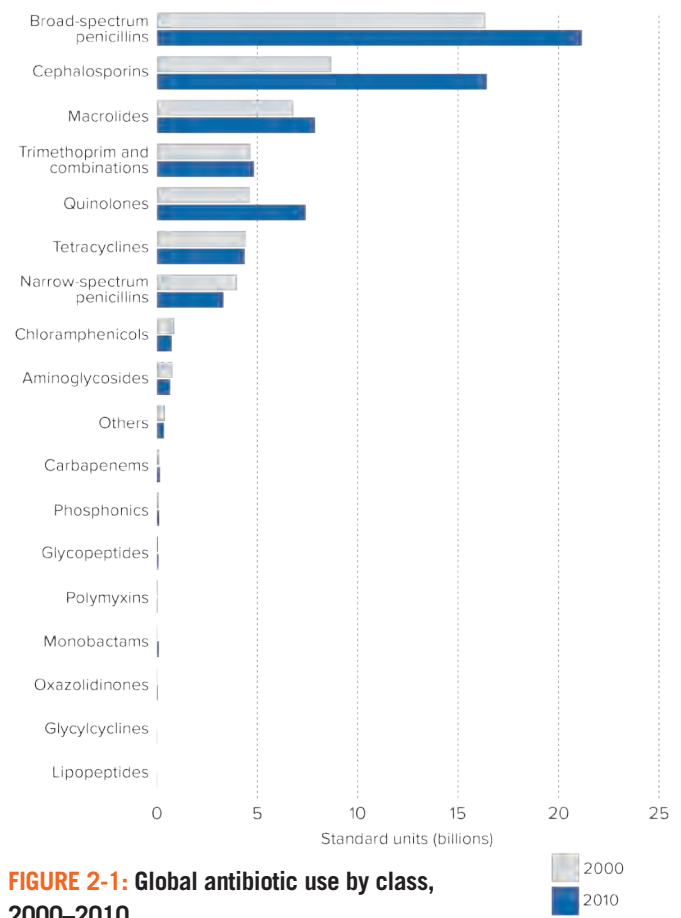


FIGURE 2-1: Global antibiotic use by class, 2000–2010

Van Boeckel et al. 2014 (adapted; based on IMS MIDAS)

representing an overall decline of 5 percent in per capita prescribing since 1999. Annual outpatient prescription rates in the United States are lower than in many Southern European nations but higher than in Scandinavia and the Netherlands (CDDEP 2015).

Most high-income countries maintained or decreased their antibiotic consumption from 2000 to 2010 (Figures 2-4, 2-5). The five rapidly growing countries known as the BRICS had the greatest upsurge in antibiotic use from 2000 through 2010: 68 percent in Brazil, 19 percent in Russia, 66 percent in India, 37 percent in China, and 219 percent in South Africa (Figure 2-6). About three-quarters of the total increase in global consumption occurred in these nations; however, they accounted for only one-third of the world's increase in population from 2000 to 2010 (Van Boeckel et al. 2014).

Even with the substantial increase in overall use, per capita consumption is still lower in the BRICS countries than in the United States. In 2010, in the United States, penicillins were the most commonly prescribed antibiotics (38 percent), followed by cephalosporins (16 percent), tetracyclines (15 percent), macrolides (12 percent),

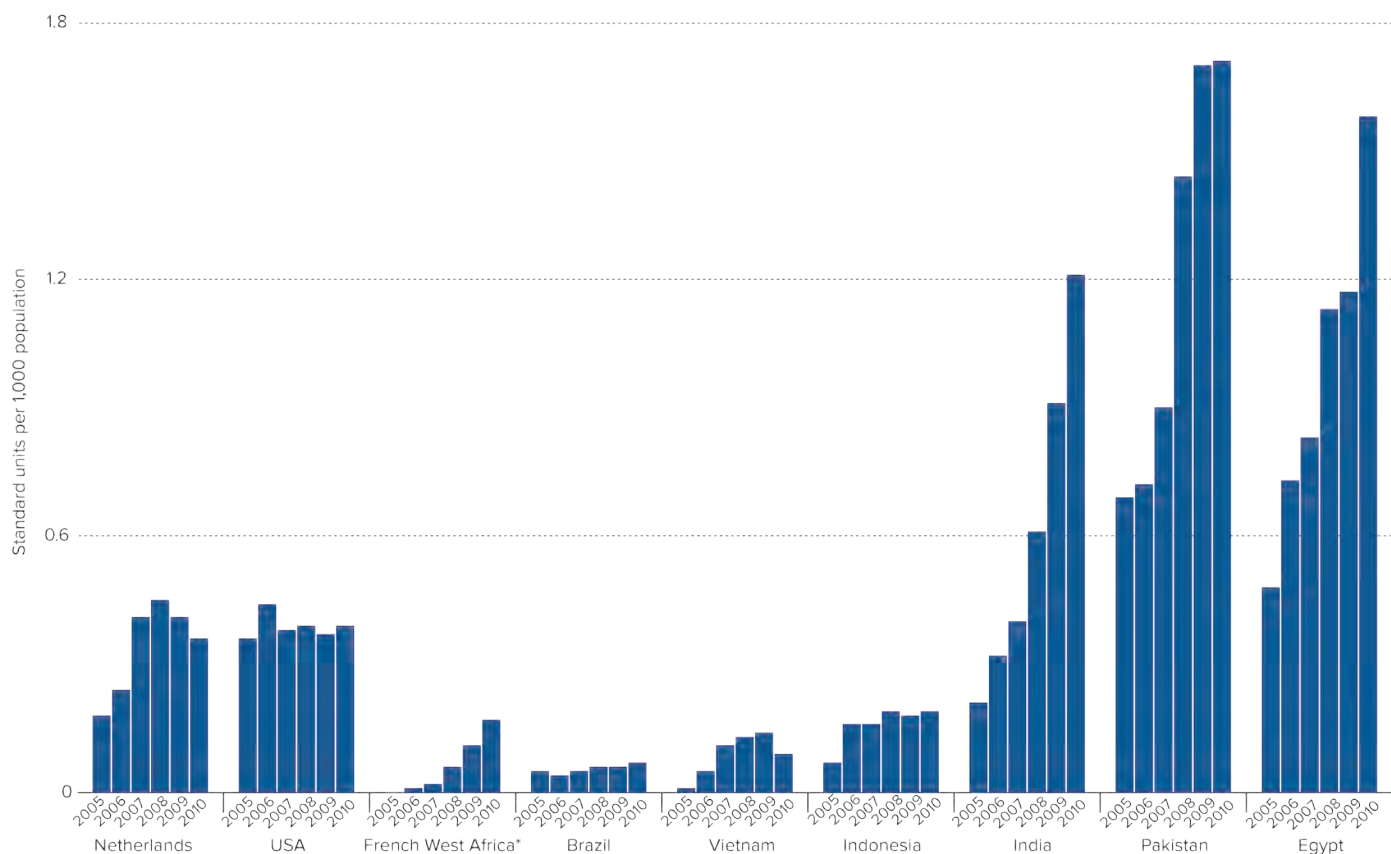


FIGURE 2-2: Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)

Source: Laxminarayan et al. 2013 (based on IMS MIDAS)

*An IMS grouping of Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo

quinolones (9 percent), and trimethoprim (10 percent) (Van Boeckel et al. 2014 (based on IMS MIDAS).

The wide range of consumption values and different patterns of change suggest that antibiotic consumption is driven not strictly by disease incidence. In the United States, for example, antibiotic prescribing rates are related to physician density

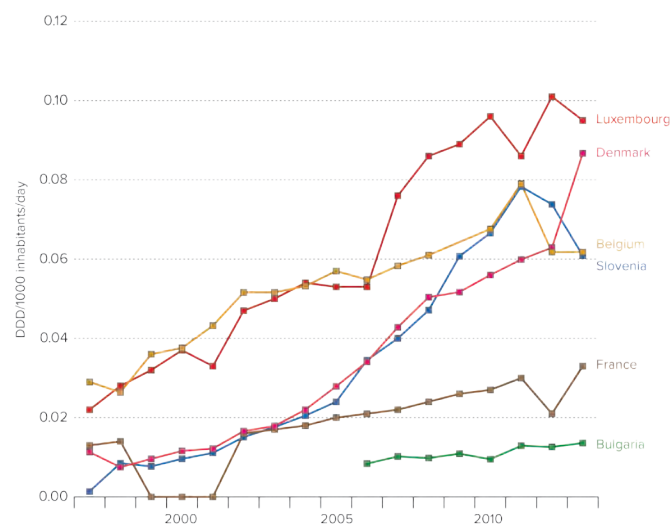


FIGURE 2-3: Carbapenem consumption in the hospital sector in selected European countries, 1997–2013

Source: ESAC-Net 2015

(measured as the number of physician offices per capita). More physicians makes it easier to get an appointment, and more visits means more antibiotic prescriptions. The difference is substantial: four additional physician offices per 10,000 people results in a 26 percent increase in prescriptions per capita. The presence of retail and urgent-care clinics also increases antibiotic prescribing, with a differential effect in wealthier and poorer areas (Klein et al. 2015). Other structural and behavioral drivers include education, access to insurance, antibiotic costs, and patient demand (Filippini et al. 2006; Matuz et al. 2006; Harbarth and Monnet 2008).

Seasonal patterns

Antibiotic use is correlated with the spread of seasonal infections, such as influenza (Polgreen et al. 2011). From 2000 to 2010, antibiotic use peaked in North America and Western Europe from December through February, in South America in June and July, and in most of the tropics from August through September (Sun et al. 2012). These patterns are consistent with a higher incidence of infectious disease during winter flu season and vector borne febrile diseases during heavy rains and monsoons (Van Boeckel et al. 2014 based on IMS MIDAS). Gram-negative bloodstream infections are more prevalent in hotter weather: independent of season, humidity, and precipitation, an increase of 10 degrees Fahrenheit (5.6°C) in monthly temperature increased the frequency of Gram-negative

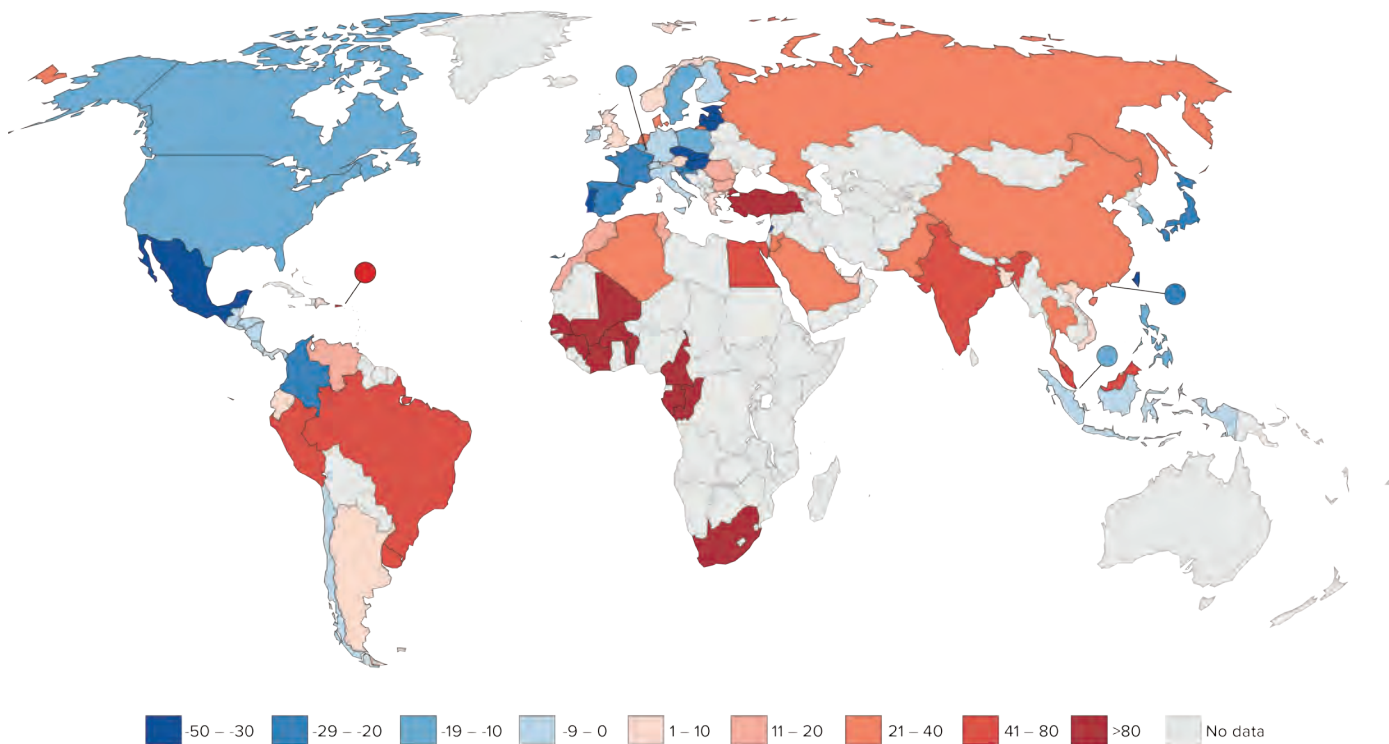


FIGURE 2-4: Percentage change in antibiotic consumption per capita 2000–2010*, by country

Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

*Data for Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama were available only as a group classified as Central America. Similarly, data for Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings they belong to. For countries that did not have data available for 2000, the values for the earliest years for which data were available after 2000 were used to calculate the percentage changes. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2005), and Vietnam (2005).

bloodstream infections by 4 and 11 percent for *E. coli* and *Acinetobacter* spp., respectively (Eber et al. 2011).

INAPPROPRIATE ANTIBIOTIC USE

From 20 to 50 percent of total antibiotic use is estimated to be inappropriate (Cizman 2003). “Inappropriate” can mean either of two things:

- the use of antibiotics when no health benefit is possible, such as to treat upper respiratory tract infections caused by viruses; or
- the suboptimal use of antibiotics for responsive conditions, such as the choice of drugs with an unnecessarily broad spectrum, an incorrect dosage or duration, or poor patient adherence to the prescribed treatment (Starrels et al. 2009).

Substandard antibiotics also contribute to antibiotic consumption with little or no benefit (see Chapter 4). Also inappropriate is antibiotic *nonuse* when an antibiotic could improve health, but clearly, the reasons for nonuse are very different. Lack of access and delayed access to antibiotics contribute significantly to morbidity and mortality worldwide. In the year 2013, pneumonia was responsible for an estimated 935,000 deaths in children under five worldwide (Liu et al. 2015).

An estimated 80 percent of all antibiotics are used outside hospitals.

SETTINGS FOR HUMAN ANTIBIOTIC USE

Antibiotics in the community

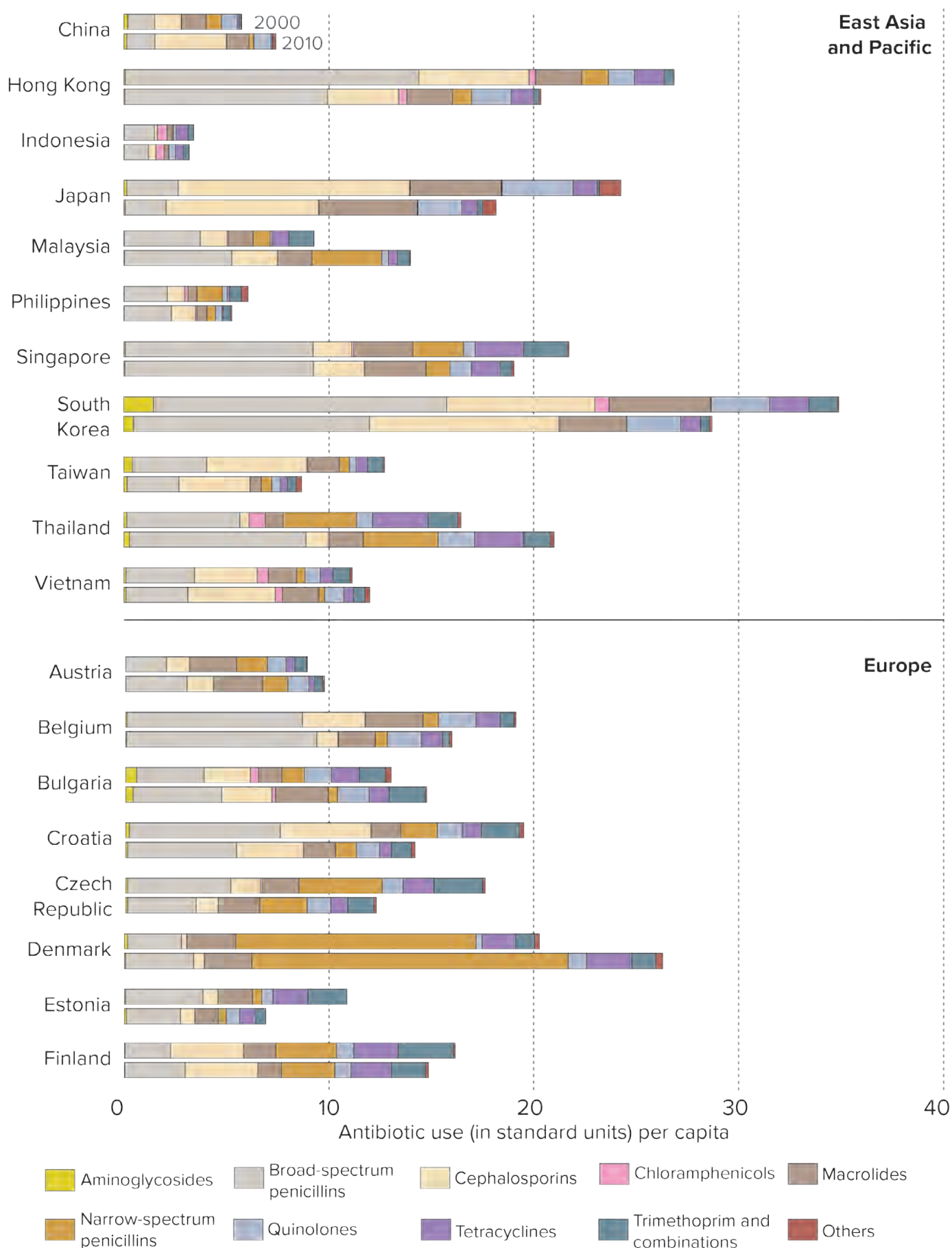
An estimated 80 percent of all antibiotics are used outside hospitals—in outpatient settings such as clinics, health posts, and private physicians’ offices (Kotwani and Holloway 2011). Community use also includes antibiotics purchased by or for consumers directly, without prescription. Although prescription-only laws exist in most countries (for at least some antibiotics), they are not enforced in most LMICs and some high-income countries.

Nonprescription use of antibiotics can range from 19 percent to well over 90 percent outside the United States and Europe (Morgan et al. 2011). In rural and urban pharmacies in Vietnam, 88 to 91 percent of all antibiotic sales in a sample of pharmacies in 2010 were without a prescription (Do Thi Thuy Nga et al. 2014). Similarly, in Saudi Arabia and Syria, 78 percent and 87 to 97 percent of pharmacies, respectively, dispensed antibiotics without a prescription (Al-Faham et al. 2011; Bin Abdulhak et al. 2011).

Providers also play a role in driving inappropriate antibiotic use in the community. Antibiotics are routinely prescribed

FIGURE 2-5: Antibiotic consumption per capita by class and country, 2000 and 2010

Source: Van Boeckel et al. 2014 (adapted; based on IMS MIDAS)



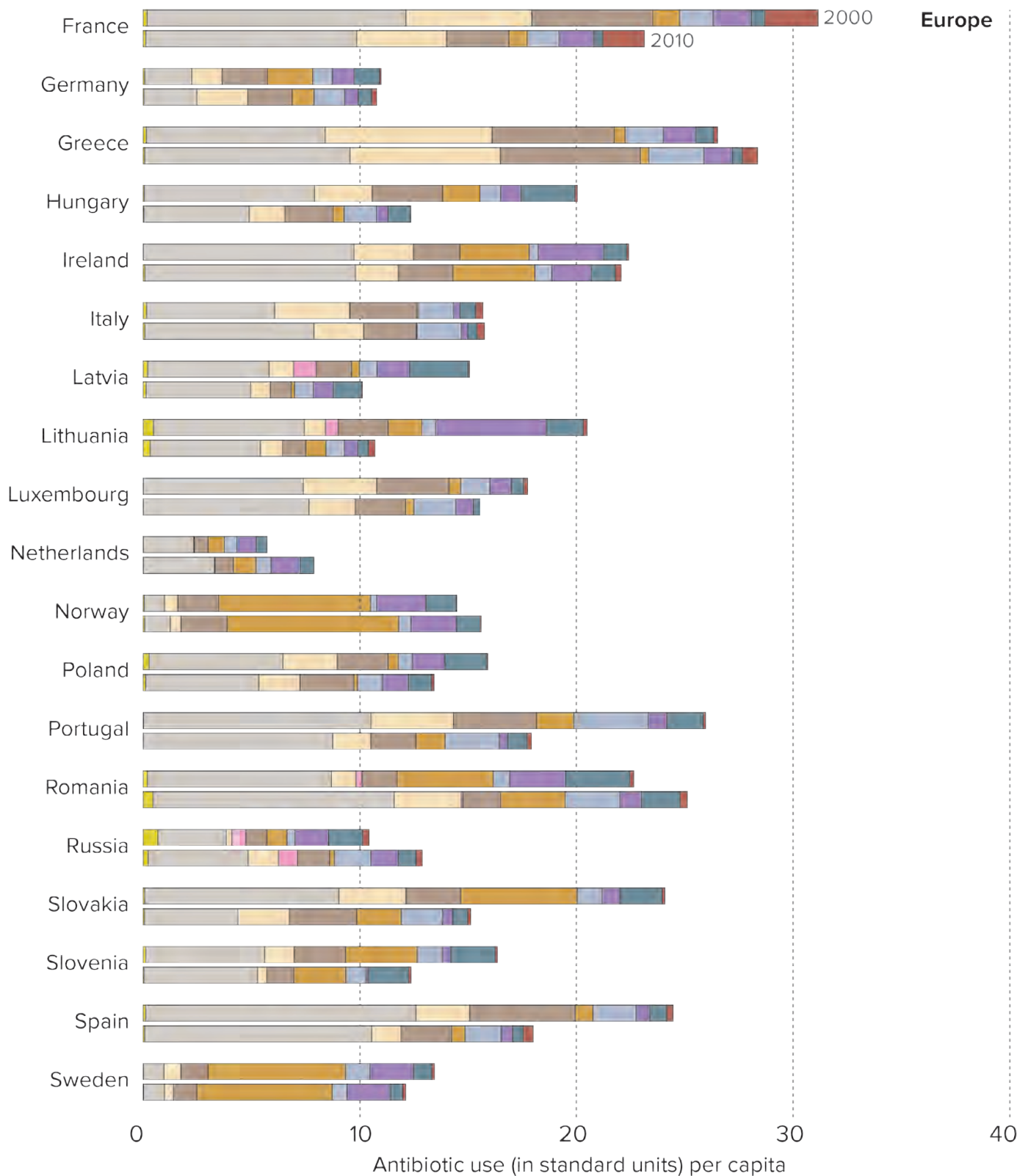
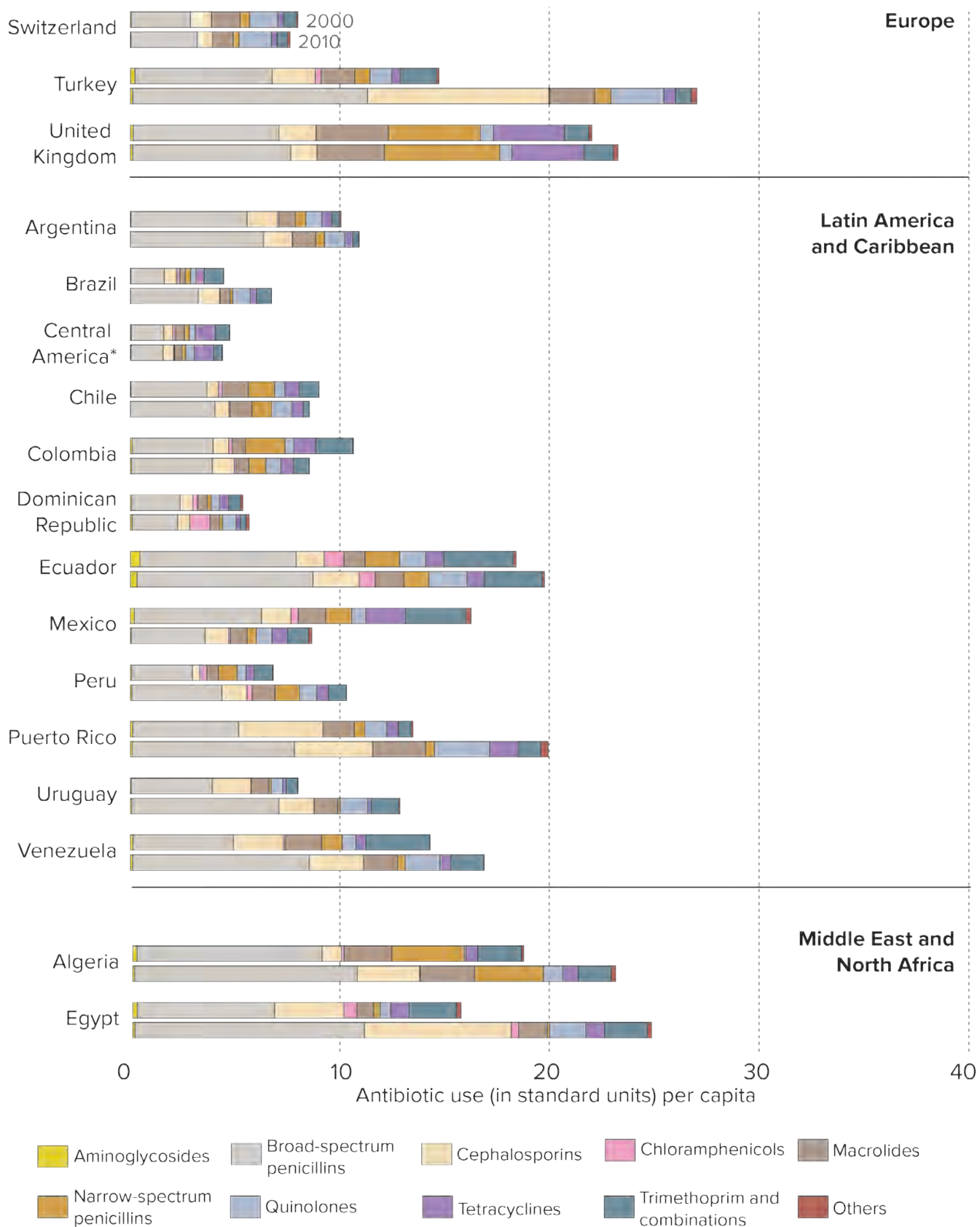
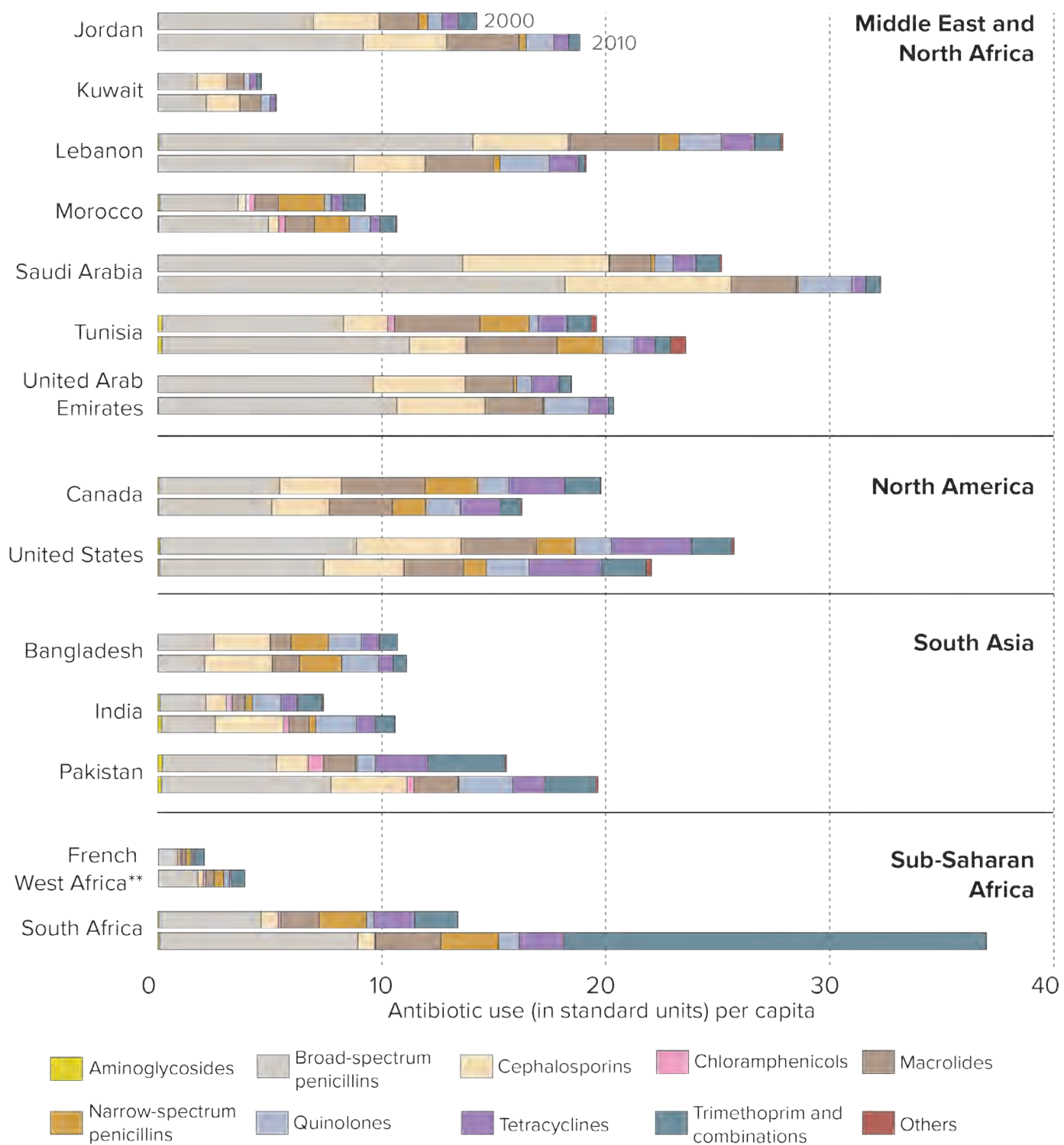


FIGURE 2-5: Antibiotic consumption per capita by class and country, 2000 and 2010, *continued*

Source: Van Boeckel et al. 2014 (adapted; based on IMS MIDAS)



*Central America grouping includes Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama.



**French West Africa grouping includes Benin, Burkina Faso, Côte d'Ivoire, Gabon, Guinea, Mali, Niger, Republic of the Congo, Senegal, and Togo. For countries that did not have data available for 2000, the earliest year for which data were available after 2000 are shown. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2005), and Vietnam (2005).

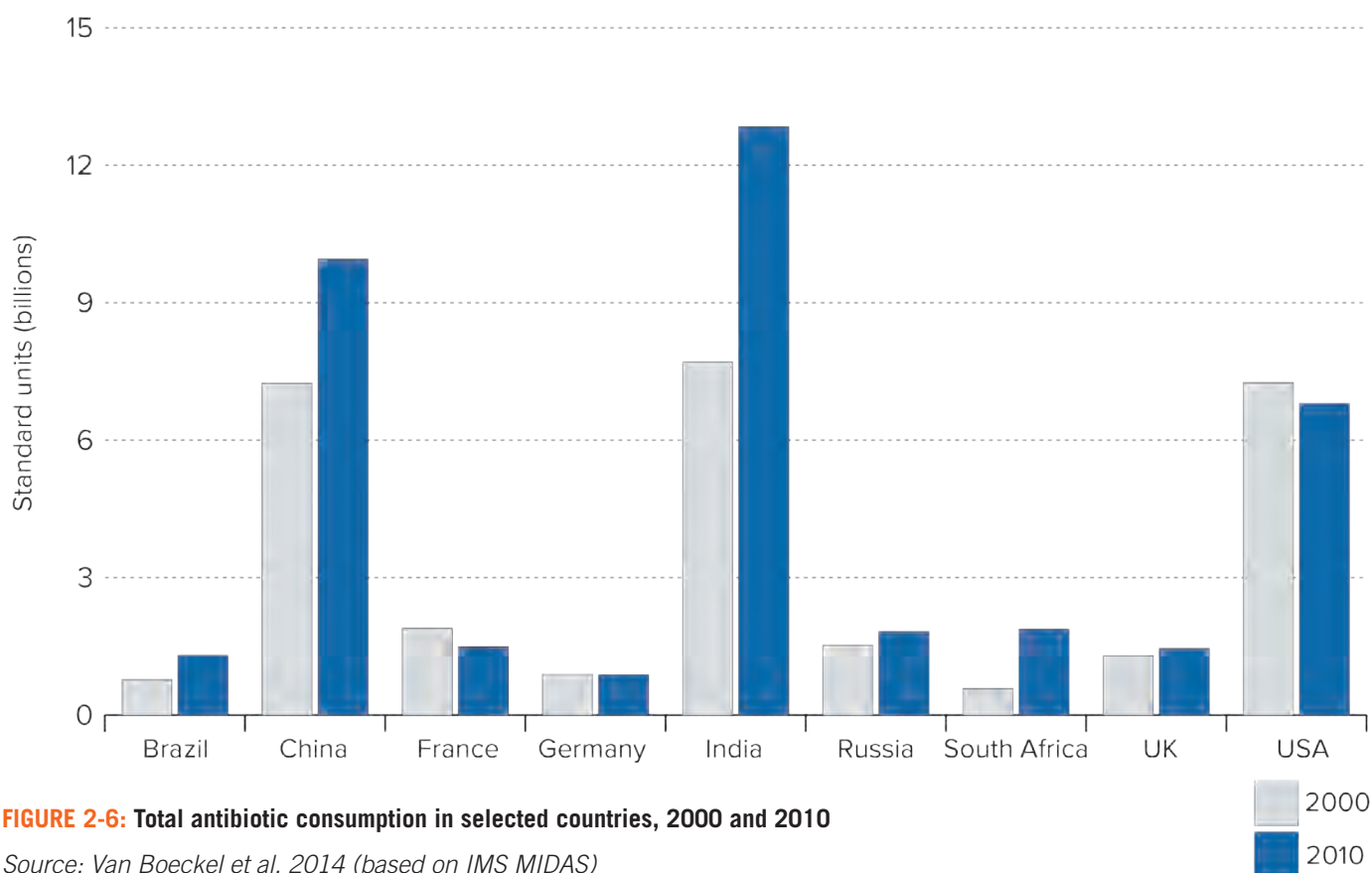


FIGURE 2-6: Total antibiotic consumption in selected countries, 2000 and 2010

Source: Van Boeckel et al. 2014 (based on IMS MIDAS)

for infections that are not caused by bacteria, such as for malaria (Means et al. 2014), acute diarrhea (Kotwani et al. 2012), influenza (Misurski et al. 2011), uncomplicated viral respiratory tract infections (Kotwani et al. 2012), and other viral infections. This may occur because of an absence of clinical training and guidelines on antibiotic treatment available to physicians, or because of a lack of diagnostics and trained personnel to conduct testing and identify the cause and susceptibility of the infection.

Private pharmacies in India dispense a wider variety of antibiotics than do public pharmacies (Sudarshan et al. 2013). Patterns of use in the private sector, at both retail pharmacies and private clinics, were similar. Newer antibiotics (such as cephalosporins and fluoroquinolones) were often used more than older ones (such as co-trimoxazole and tetracyclines). At public facilities, while the newer members from each class of antibiotic were also used, there was greater use of older antibiotics—co-trimoxazole, tetracyclines, and narrow-spectrum penicillins—than in the private sector (Kotwani and Holloway 2011). Patient demand can affect drug selection as well: in South India, a hospital pharmacy stocked 25 brands of cotrimoxazole in response to customers' requests for specific name-brand products (Nichter and Vuckovic 1994).

Antibiotics in hospitals

In hospitals, even when a specific pathogen is identified, many patients are still given broad-spectrum antibiotics. Because these drugs are effective against a wide range of pathogens, they may contribute to the spread of resistant

strains of many nontarget organisms. In a study involving six U.S. hospitals in 2009 and 2010, only 59 percent of patients received appropriate cultures, and by the fifth day of therapy, 66 percent of antimicrobial therapy regimens were unchanged, despite negative cultures in 58 percent of patients (Braykov et al. 2014). In addition, 30 percent of the patients were afebrile and had a normal white blood cell count at the start of antibiotic therapy. These results indicated that broad-spectrum antimicrobial therapy was commonly prescribed to inpatients even when clinical signs of infection were not present, and this treatment was not de-escalated or discontinued even when cultures did not show evidence of bacterial infection. In 2010, 56 percent of hospitalized patients in 323 hospitals across the United States received an antibiotic during their stay, often broad-spectrum agents. Among patients who received an antibiotic, 37 percent of treatments could have been improved, primarily through better use of diagnostic tests (Fridkin et al. 2014).

Overuse of antibiotics in hospital settings is also common in LMICs. For instance, rates of inappropriate prescribing of antibiotics in hospitals in Nepal range from 10 to 42 percent (Paudel et al. 2008; Shankar et al. 2007; Shankar et al. 2006). Nepali hospitals also report low rates of bacterial cultures, and antibiotics are frequently the most commonly prescribed medication. In Vietnam, one-third of hospital prescriptions were inappropriate. Risk factors associated with inappropriate prescriptions in Vietnam included surgical wards, obstetrics and gynecology departments, and national hospitals (Thu et al. 2012).

Seven times more antibiotics are used when they are given post- rather than pre-surgery.

Although presurgical antibiotics are the evidence-based standard in high-income countries for preventing postsurgical infections, they are commonly given *after* surgical procedures in many LMICs, which have a higher risk of surgical site infections (Aiken et al. 2013). Seven times more antibiotics are used when they are given post- rather than pre-surgery. This increases costs and contributes to the potential for antibiotic resistance (Aiken et al. 2013). Even when antibiotics are administered before surgery, the regimen or duration of the therapy may be suboptimal: from 19 to 86 percent of patients in hospitals in India received inappropriate antibiotic prophylaxis (Belagali et al. 2013; Rana et al. 2013; Rehan et al. 2010). In addition to preoperative antibiotic prophylaxis, improved hygiene and better surgical techniques can decrease rates of surgical site infections in developing countries (Aiken et al. 2012, 2013).

CAMPAIGNS TO REDUCE INAPPROPRIATE ANTIBIOTIC USE

Increasing both healthcare workers' and patients' awareness about antibiotic resistance through regional or national awareness campaigns can help change behavior and reduce inappropriate prescribing.

Two of the best known national campaigns took place in France and Belgium. In France, which once had the highest rate of antibiotic consumption in Europe, the government launched an awareness campaign called "Antibiotics are not automatic" as a part of a program to preserve antibiotic effectiveness. The campaign, which was launched in 2001, achieved a reduction in antibiotic prescribing of 27 percent over five years in all regions of the country, with the greatest decline, 36 percent, in children 6 to 15 years of age (Sabuncu et al. 2009). In Belgium, the Belgian Antibiotic Policy Coordination Committee established a national media campaign in 2000 that succeeded in reducing antibiotic prescribing by 36 percent over seven years (Goosens et al. 2008).

Most public campaigns to reduce community antibiotic use in high-income countries have focused on eliminating use for respiratory tract infections (Huttner et al. 2010). These campaigns

- were multifaceted, most targeting the general public, particularly parents of young children;
- involved the participation of health authorities;
- received public funding; and
- lasted at least one year (Table 2-1).

Some campaigns have been tied to broader strategies to reduce resistance, and most included components targeting healthcare providers, hospitals, or both. Messages have been conveyed through printed materials sent to healthcare providers and pharmacists for distribution in their offices, in addition to mass media and the Internet. Other approaches to reaching healthcare providers were intensive academic detailing, audits, feedback, and guidelines (Huttner et al. 2010).

In Belgium,...a national media campaign... succeeded in reducing antibiotic prescribing by 36 percent over seven years.

Most campaigns were not designed as trials that could be easily evaluated for either changing behavior or the ultimate goal, reducing antibiotic resistance. It is clear that at least some campaigns were effective in changing behavior in the short term. In France and Belgium, close to two-thirds of surveyed family doctors reported reduced antibiotic prescribing after a campaign. France and Belgium also saw some decreases in penicillin and macrolide resistance in pneumococci following their campaigns (Sabuncu et al. 2009; Goosens et al. 2008). Future campaigns should be based on determinations of which interventions and approaches are most effective.

CONCLUSIONS

Antibiotic use in humans is increasing worldwide for first-line and some last-resort antibiotics. High-income countries tend to use more antibiotics per capita than LMICs, but consumption in most appears to be stabilizing or decreasing. The highest rates of increase are in middle-income countries, particularly the BRICS, a trend that is likely to continue as incomes continue to rise. Variation in use indicates that consumption is driven by factors other than disease and demography, such as seasonality, economic growth, and access.

Inappropriate antibiotic use is driven by both healthcare workers and consumers, particularly in the community, where 80 percent of antibiotic consumption takes place. In hospitals, the suboptimal use of broad-spectrum and postsurgical antibiotics remains prevalent. Interventions targeting these areas could significantly reduce global use. However, lack of or delayed access to antibiotics still kills more people than resistant infections. To achieve the maximum benefits to human health, measures to reduce inappropriate use of antibiotics must be combined with efforts to improve access when they are needed.

TABLE 2-1: PUBLIC CAMPAIGNS TO IMPROVE USE OF ANTIBIOTICS IN OUTPATIENTS

Country, year	Campaign name or slogan	Organization	Approximate cost per year	Interventions	Comments
Australia, 2000–08	Common colds need common sense, not antibiotics	Agency of department of health	AU\$100,000 in 2003, \$800,000 in 2007	Pamphlets, posters, print media, billboards,† radio, television, website, letters, guidelines, seminars, academic detailing	Varying seasonal use of mass media, physicians targeted via separate program since 1999, focus on “common cold”
Belgium, 2000– (except 2003–2004)	Antibiotics are ineffective for the common cold, acute bronchitis and flu	Committee established by department of health	€400,000	Pamphlets, posters, print media, radio, television,‡ website,‡ letters, guidelines, academic detailing	Yearly seasonal use of mass media, individual feedback about prescribing behavior (2001, 2003, 2006, 2007)
Canada, 1996–2006	National information program on antibiotics	Coalition of professional societies and pharmaceutical industry	CA\$50,000–300,000\$, entire funding provided by Pfizer	Pamphlets, posters, print media, radio, letters	Limited seasonal use of mass media, advertisements in professional publications targeting physicians and pharmacists
France, 2002–	Antibiotics are not automatic	National health insurance	€22,500,000 in 2002–2004	Pamphlets, posters, print media, radio, television,‡ website,‡ letters, guidelines, seminars, academic detailing‡	Yearly seasonal use of mass media, internet campaign and travelling exhibition, intensive academic detailing for high-prescribing physicians, promotion of streptococcal rapid antigen test, special daycare program
Germany 1, 2000–	Explosive antibiotic resistance	Coalition of professional societies in field of infectious diseases	—	Pamphlets, posters, website‡	Very limited campaign consisting of website and mailing of informational material on request, physicians not targeted
Germany 2, 2007–	Informational campaign on antibiotic resistance	Private foundation	§	Pamphlets, posters, print media, website, seminars	Very limited campaign using mainly website and distribution of “antibiotic passport,” promotion of herbal remedies as alternative to antibiotics
Greece, 2001–03	For the prudent use of antibiotics	Agency of department of health	—	Pamphlets, posters, radio, television, website, letters, guidelines, seminars,	Two seasonal campaigns with limited use of mass media (TV, radio broadcast by state channels free of charge)
Iceland, 1991–1998	(Untitled)	Not centrally organized	—	Pamphlets, posters, letters, guidelines, seminars	Public information provided by key stakeholders and opinion leaders (e.g., interviews on TV, media conferences)

TABLE 2-1: PUBLIC CAMPAIGNS TO IMPROVE USE OF ANTIBIOTICS IN OUTPATIENTS

Country, year	Campaign name or slogan	Organization	Approximate cost per year	Interventions	Comments
Israel, 2001, 2003, 2006	Antibiotic campaign	Health maintenance organization	—	Pamphlets, posters, billboards, † radio, television, ‡ website, letters, guidelines	Three seasonal campaigns with use of mass media organized by Israel's second-largest health maintenance organization, distribution of informational material only to physicians contracting with health maintenance organization
Luxembourg, 2004–2005, 2006–2007, 2008–2009	Awareness campaign for the appropriate use of antibiotics	National department of health	€50,000	Pamphlets, posters, billboards, † radio, television, ‡ website, letters, guidelines	Seasonal campaign every other year with use of mass media
Malta, 2003–2004	Antibiotics do not cure every infection	Committee established by department of health	€10,000	Pamphlets, posters, billboards, † website, guidelines, seminars	Single seasonal campaign with limited use of mass media, focus on self-medication and over-the-counter use
New Zealand, 1999–	Wise use of antibiotics	Government agency	NZ\$100,000–170,000 in 1999–2006, \$450,000 in 2007	Pamphlets, posters, radio, television, ‡ website, † letters, guidelines	Multiyear seasonal campaign with use of mass media only since 2007
Norway, 2004	Appropriate antibiotic use—for the child's best interest	Institute of public health	—	Pamphlets, posters, website, letters, seminars	Single seasonal campaign focusing on young children without use of mass media
Portugal, 2004–2007	Antibiotics, use them in an adequate way	Coalition of pharmaceutical industry, department of health, professional organizations	€60 000\$, entire funding provided by Pfizer	Pamphlets, posters, print media, radio, website, † letters	Three seasonal campaigns with limited use of mass media
Spain, 2006–2008	Campaign for the responsible use of antibiotics	National department of health	€6,500,000 in 2006, €5,000,000 in 2007	Pamphlets, posters, print media, billboards, † radio, television, ‡ website, † letters, guidelines, seminars	Two seasonal campaigns with intensive use of mass media, focus on self-medication and over-the-counter use
United States, 1995–	Campaign for appropriate antibiotic use in the community (1995–2002); Get Smart: know when antibiotics work (2003)	Agency of department of health	US\$30,000–100,000 per state	Varies by state	Federal funding distributed by CDC to state health authorities for development, implementation, and evaluation of local campaigns; national media campaign in 2003; varying number of funded states each year (e.g., 34 in 2006, 13 in 2009)

Adapted from “Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries”, Huttner 2010

Where no reference is cited, the information was obtained from campaign managers, campaign websites, and other unpublished material.

*English translation if originally in another language.

†Billboards or public transport advertisements.

‡Intensive use of the intervention: prime-time TV, independent website, intensive academic detailing (i.e., more than few dozen physicians).

§Some funding provided by pharmaceutical industry.

KEY MESSAGES

- As global demand for animal protein grows, antibiotics are increasingly used to raise food-producing animals in intensive production—mostly to promote growth rather than treat disease. The result is an increasing prevalence of antibiotic-resistant bacteria in livestock, poultry, and aquaculture, with spillovers that affect human health.
- Livestock farmers must be provided the knowledge and tools to optimize production systems without antibiotic growth promoters and to minimize antibiotic use for disease prevention.
- We recommend phasing out sales of feed pre-mixed with antibiotics and reducing the use of antibiotic metaphylaxis in all countries.

Antibiotics have been used to treat infections in animals for as long as they have been widely available. They also have a surprising ability to accelerate animal growth. Currently, more antibiotics are used in poultry, swine, and cattle to promote growth and prevent disease than are used by the entire human population. Though the figure is based on incomplete data, an estimated 80 percent of all antibiotics consumed in the United States are used in food animals (U. S. FDA 2010).

As global demand for animal protein continues to accelerate, fueled by a growing population and rising incomes in low- and middle-income countries (LMICs), antibiotic use will continue to rise unless steps are taken to reduce the need for them by helping countries optimize production systems, as has been done in high-income countries. Information on antibiotic use in animals, scant in high-income countries, is even less available in LMICs, where regulation and control are not well developed.

Significant amounts of the antibiotics used by people and animals eventually find their way into the environment, particularly in surface and ground water and in soil. Antibiotic-resistant bacteria arise and spread in animals and in the environment and may cause human disease. The situation is particularly acute where clean water and adequate sanitation are not available.

ANTIBIOTIC USE IN AGRICULTURE

The projected increase in antibiotic use in food animals is a result of an increase in human population, from 7 billion today to an expected 9 billion to 10 billion by 2050, and increasing global prosperity. Demand for meat and other animal products is predicted to nearly double in the next 35 years. According to the United Nations Food and Agriculture Organization (FAO), meat consumption will increase by 73 percent and dairy consumption by 58 percent over 2011 levels (FAO 2011). Most of the population growth and even more of the growth in food demand will come from sub-Saharan Africa and Asia, as rising incomes allow those populations to increase their caloric intake and improve the quality of food.

...more antibiotics are used in poultry, swine, and cattle to promote growth and prevent disease than are used by the entire human population.

We know from the European and U.S. experience that antibiotic use in animals can be limited with minimal effects on production. If other inputs (including breeding) are optimized, antibiotics add very little in terms of growth promotion.

The other major use of antibiotics, to prevent disease, can be reduced by improved farm hygiene and public health measures, particularly animal vaccines. A global priority is to ensure that as they increase productivity by adopting intensive farming models, countries do not greatly increase their antibiotic use.

Antibiotics have three roles in animal production: to treat individual animals with bacterial infections, to prevent infections, and to promote growth. The first two roles are no different from uses in humans, where the drugs are used to treat and prevent infections (e.g., before major surgery, to prevent infection of the surgical site). In animals, however, antibiotics may be given to entire flocks or herds to prevent an infection from sweeping through the animal population at vulnerable points in the production cycle, such as the weaning of young pigs from sows. Antibiotic use may be triggered by an infection in one or more animals, or by a history of a particular infection at a precise stage of development. These prophylactic or “metaphylactic” antibiotics are usually mixed with water or food.

The third role, growth promotion, has no counterpart in human antibiotic use. It accounts for the majority of use in animals and is the focus of most legal and regulatory efforts to reduce antibiotic consumption in livestock and poultry. Growth promotion is accomplished with ultralow doses of antibiotics mixed with feed by the manufacturer or the farmer.

Type and extent of use

Chickens and pigs consume most of the antibiotics used in food animals around the world. The amount of antibiotics used in aquaculture worldwide is also potentially significant. Antibiotics are also used in beef cattle in the United States, Brazil, and

Argentina, where the animals are “finished” in large feedlots (Millen et al. 2011). In the United States, about three-quarters of feedlots administered at least one antibiotic for growth promotion or disease prevention in 2011 (USDA 2013). Sheep, dairy cows, and cattle raised without feedlots consume much smaller amounts of antibiotics, as do companion animals.

Most antibiotics used in animal production are similar to those used in the human population: of the 27 antimicrobial classes that are used in animals, only nine are used exclusively in animals (Pagel and Gautier 2012). The top three classes by global sales for animal use in 2009 were macrolides (\$600 million), penicillins (\$600 million), and tetracyclines (\$500 million), all of which are categorized as critically important in human medicine (WHO 2011b).

Aquaculture is a booming industry around the world, particularly in Asia—mainly China—the source for 80 to 90 percent of the world’s shrimp and carnivorous fish (Marshall and Levy 2011). In the Americas, Chile is a major producer of salmon, which is raised with at least a dozen antibiotics, including a large amount of quinolones (Marshall and Levy 2011). These antibiotics not only promote resistant bacteria in the farmed fish but also transmit resistance to wild fish populations and the broader environment.

One of the difficulties in evaluating the use and effects of antibiotics in livestock is the lack of reliable information on global use. Some information is available for high-income countries, however. Combining these data with global livestock density maps, CDDEP researchers (Van Boeckel et al. 2015) applied statistical models to estimate global antibiotic use in poultry, swine, and cattle in 2010. Expected antibiotic consumption in 2030 was estimated using projections of livestock product consumption, including some shifts from extensive (i.e., small-scale) husbandry to intensive (i.e.,

Consumption in Brazil, Russia, India, China, and South Africa (the BRICS) is expected to double by 2030 as their population increases by 13 percent.

industrial-scale) farming systems, which rely more heavily on antibiotics for growth promotion and disease prevention.

Global antibiotic consumption in livestock was conservatively estimated at 63,200 tons in 2010 (van Boeckel et al. 2015), accounting for nearly two-thirds of the estimated 100,000 tons of antibiotics produced annually worldwide (Bbosa and Mwebaza 2013). By 2030, consumption is projected to rise by two-thirds, to 105,600 tons. Two-thirds of the increase is due to increases in the number of animals, and the remaining one-third is due to the shift from extensive to intensive farming (van Boeckel et al. 2015) (Figure 3-1).

In 2010, China was estimated to consume the most antibiotics in livestock, followed by the United States, Brazil, Germany, and India (Figure 3-2). The pattern is similar for projected antibiotic consumption in livestock in 2030, with Mexico replacing Germany in the top five countries. Consumption in Brazil, Russia, India, China, and South Africa (the BRICS) is expected to double by 2030 as their population increases by 13 percent (Van Boeckel et al. 2015).

The greatest uncertainty about current use patterns in livestock is in the low-income countries. More effort is needed to investigate the current practices of antibiotic use in animal production and to provide appropriate guidance for increasing production without the use of antibiotics (Box 3-1).

ANTIBIOTIC RESISTANCE RATES IN FOOD ANIMALS

No global picture of antibiotic resistance in food animals exists. National-level surveillance data from the United States

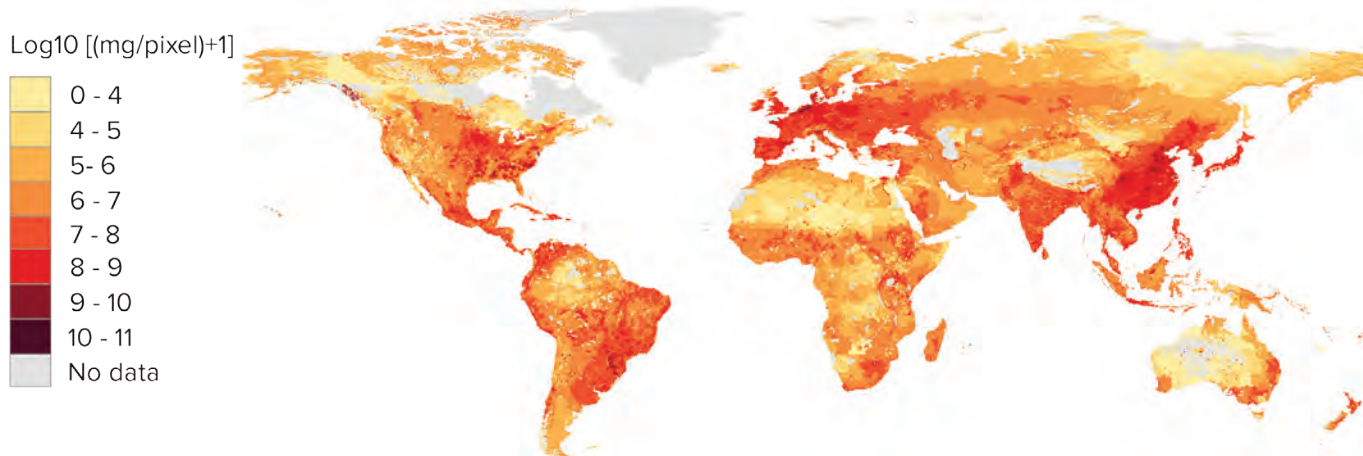


FIGURE 3-1: Global antibiotic consumption in livestock (milligrams per 10 km² pixels) 2010

Source: Van Boeckel et al. 2015

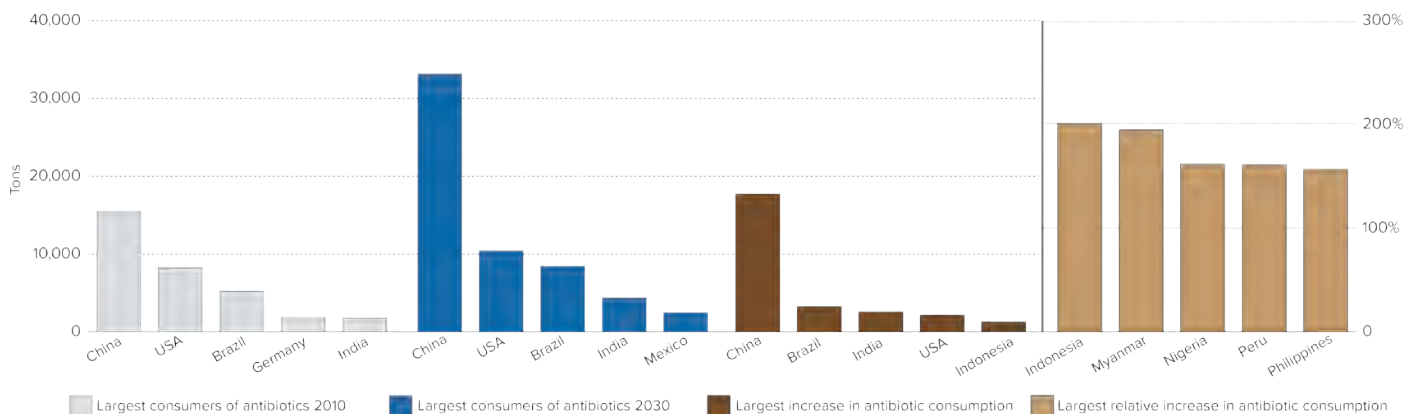


FIGURE 3-2: Antibiotic consumption in livestock in high-consuming countries, 2010–2030 (projected for 2030)

Source: Van Boeckel et al. 2015

(NARMS 2011) and Europe (EFSA and ECDC 2015) are collected routinely. The most recent published data from these systems are summarized in Table 3-1.

The European Food Safety Authority, the European Commission, and the European Centre for Disease Prevention and Control (ECDC) routinely compile surveillance reports on antibiotic resistance in food animals from member countries. Resistance rates are reported for bacterial isolates from poultry, swine, and cattle, including *Salmonella*, *Campylobacter*, *Escherichia coli*, and in some cases, methicillin-resistant *Staphylococcus aureus* (MRSA).

Since 1996, the U.S. National Antimicrobial Resistance Monitoring System (NARMS), a collaboration of the Food and Drug Administration (FDA), the Centers for Disease

Control and Prevention (CDC), and the U.S. Department of Agriculture, has collected reports of antibiotic resistance among bacterial isolates from swine, cattle, chickens, and turkeys at slaughter, including non-Typhi *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococcus*. Significant levels of resistance are reported for most types of animal and most antibiotics, but the patterns vary considerably.

In Europe, moderate to high resistance of *Salmonella* to tetracyclines (4 to 85 percent in poultry and 72 to 91 percent in swine) and sulfonamides (5 to 85 percent in poultry and 76 to 91 percent in swine) is reported, with similar or slightly lower resistance levels detected to ampicillin (5 to 98 percent in poultry and 77 to 87 percent in swine). Resistance to cephalosporins was low in the European Union with the exception of four countries (0 to

BOX 3-1. ANTIBIOTIC USE AND RESISTANCE IN LIVESTOCK IN KENYA

Almost all information about antibiotic use in livestock comes from high-income countries. To help design a strategy for antibiotic use and to understand the dynamics of antibiotic use in a low-income country, researchers at the Global Antibiotic Resistance Partnership–Kenya studied beef cattle, poultry, and swine production and tested meat samples for antibiotic-resistant bacteria. Through laboratory analyses and interviews with farmers, veterinarians and other animal health professionals, government livestock specialists, and retailers of veterinary products, Irungu (2011) created a snapshot of the situation in Kenya.

Antibiotics were freely used by farmers in all types of animals, and for the most part, farmers decided on their own when to use them—not unlike the common practice of self-prescribing by the human population in Kenya. Antibiotics were being used mainly for treatment and prevention, not intentionally for growth promotion. However, because farmers often used antibiotics at subtherapeutic levels, the drugs may have acted similarly to growth promoters.

Farmers were aware that better sanitation and hygiene measures were good alternatives to antibiotics and were more affordable. The cost of antibiotics was a clear consideration—perhaps more so than in high-income countries—in decisions about their use. Vaccines provided by the government appeared to reduce antibiotic use, but provision of free antibiotics by certain nongovernmental organizations increased use.

In the laboratory, high levels of antibiotic-resistant bacteria were found in all types of animal products. The patterns of resistance were consistent with patterns of use by farmers. The highest resistance levels were recorded for the most frequently used antibiotics: tetracyclines, sulfonamides, penicillins, and streptomycins.

This study was the first of its kind in Kenya, completed on a modest budget. It demonstrates the feasibility of collecting reliable information that can be used to prioritize concerns associated with antibiotic use in animals, to inform policymakers about the issue, and to develop plans for ongoing surveillance, even if at a limited scale.

TABLE 3-1. PERCENTAGE OF ANTIBIOTIC-RESISTANT ISOLATES IN FOOD-PRODUCING ANIMALS IN EUROPE (2013, IN GREY) AND UNITED STATES (2011, IN ORANGE)

Bacteria	Antibiotics tested and percentage of isolates resistant*										
	Ampicillin (penicillins)	Cefotaxime or ceftriaxone (US) (3rd-gen ceph)	Chloramphenicol (phenicol)	Ciprofloxacin (quinolone)	Gentamicin (aminoglycoside)	Nalidixic Acid (quinolone)	Sulfonamides or sulfisoxazole (US) (cephems)	Tetracycline (tetracycline)	Streptomycin (aminoglycoside)		
Salmonella spp.											
Poultry (domestic fowl, turkeys)	5-98	0-10	0-12	10-98	1-85	10-97	5-85	4-85			
Swine	77-87	0-1	12-28	6-7	4-8	3	76-91	72-91			
Poultry (chickens, turkeys)	7-27	6-12	1	0	4-17	0	8-22	41-46	22-36		
Swine	11	2	7	0	0	0	18	41	19		
Cattle	17	14	18	2	2	2	20	31	19		
Campylobacter spp.											
Poultry (broilers)	55-69	0-14	0-2	52-64	41-70						
Swine	31	21	2	31	72						
Cattle	36	1	1	36	30						
Chickens	19-28	1-3	0-6	19-28	42-45						
Escherichia coli											
Poultry	55	6	15	56	6	52	45	43	46		
Swine	30	1	15	6	2	4	42	53	48		
Cattle	14	1	8	5	2	5	20	23	18		
Chickens	16	10	2	0	49	2	55	48	51		
Enterococcus spp.											
Poultry (broilers, laying hens)	0-23	0-2	10-61	0-2	0	74	33-37	8-76	0-1		
Swine	0-9	0-25	22-59	0-11	0-2	86-95	2-34	29-87	0-2		
Cattle	0-11	0-59	0-76	0-10	0-2	64-88	0-27	0-83	1-2		
Chickens	7	2	66	28	0	86	19	77	2**		
S. aureus**§	Various antibiotics—										
	MRSA										
Poultry	0-86										
Swine	21-98										
Cattle	0-72										

*Data are presented as ranges when multiple rates were provided (e.g., for multiple strains of bacteria or multiple species of poultry). EU data include 28 countries overall, but for many bacteria, data were available from only a small subset of countries.

** Intermediate resistance only.

§ heavily weighted by results from Slovakia.

10 percent in poultry and 0 to 1 percent in swine) (EFSA and ECDC 2015). The United States has seen high rates of *Salmonella* resistance, particularly to penicillin (7 to 27 percent in poultry, 11 percent in swine, and 17 percent in cattle), sulfonamides (8 to 22 percent in poultry, 18 percent in swine, and 20 percent in cattle), and tetracyclines (41 to 46 percent in poultry, 41 percent in swine, and 31 percent in cattle) (NARMS 2011).

High proportions of *Campylobacter* from all types of animals in the United States and Europe were resistant to most of the antibiotics tested. In Europe, resistance levels in poultry were lowest to macrolides and aminoglycosides (0 to 14 percent) but higher to quinolones and tetracyclines (41 to 70 percent). In swine, resistance was highest to tetracycline (72 percent) and lowest to aminoglycosides (2 percent). In cattle, resistance was moderate to quinolones and tetracyclines (30 to 36 percent) and lowest to macrolides and aminoglycosides (1 percent) (EFSA and ECDC 2015). In the United States, resistance in poultry was slightly lower but followed similar patterns to European poultry: lowest to macrolides and aminoglycosides (0 to 6 percent) and higher to quinolones and tetracyclines (19 to 45 percent) (NARMS 2011).

In Europe, resistance was highest to most drugs in poultry, ranging from a low of 6 percent to both cephalosporins and aminoglycosides, respectively, to more than 50 percent for penicillins (55 percent) and quinolones (52 to 56 percent) (EFSA and ECDC 2015). In the United States, resistance in poultry ranged from 0 to 2 percent to quinolones and phenicols and was highest to sulfonamides, at 55 percent (NARMS 2011).

Resistance to quinupristin/dalfopristin was high in isolates of *Enterococcus* from all animals in both the United States and Europe, ranging from 64 to 95 percent across all animals in both countries. Almost no resistance to vancomycin or linezolid was reported, with rates between 0 and 2 percent for both drugs. Levels varied for all other antibiotics, with high rates for tetracyclines (from 0 to 87 percent in Europe and at 77 percent in the United States) (EFSA and ECDC 2015; NARMS 2011).

For LMICs, reports produced by the Global Antibiotic Resistance Partnership (GARP) include reviews of the resistance literature. However, the literature in these countries consists of a relatively small number of studies, leaving large gaps in knowledge of resistance levels. Major findings are summarized here.

In Nepal, bacterial isolates from poultry in 2011 to 2012 showed 100 percent resistance to bacitracin, and resistance to gentamicin, cotrimoxazole, and cephalosporins exceeded 75 percent. In 2009, complete resistance to ampicillin was reported in salmonellosis cases in poultry, in addition to high resistance to cefotaxime. In hatcheries in 2012, 93 percent of *E. coli* isolates were resistant to amoxicillin, and resistance to erythromycin, tetracyclines, and enrofloxacin was reported to exceed 50 percent. Among cattle, bacterial mastitis isolates in 2011 and 2012 showed resistance to oxytetracycline, cotrimoxazole, and amoxicillin and ampicillin. *E. coli* samples from buffalo meat showed

complete resistance to ampicillin. MRSA prevalence in milk samples from cattle in Pokhara Valley was 11 percent (GARP–Nepal National Working Group 2014).

In Uganda, staphylococcal isolates from cattle with mastitis showed high resistance to penicillin and methicillin. *Enterococcus* isolates from various food animals showed resistance of 14 to 65 percent, and the prevalence of multidrug resistance was 60 percent. Several studies also reported resistance in wild animals, such as vervet monkeys, chimpanzees, and gorillas (GARP–Uganda National Working Group, in press).

In Tanzania, resistance in bacteria causing mastitis in lactating cattle demonstrated high resistance to penicillin G, chloramphenicol, streptomycin, and oxytetracycline. Resistance of *C. jejuni* in ducks was high to ampicillin, tetracyclines, and cefuroxime (82, 74, and 48 percent, respectively). *E. coli* resistance in chickens was highest to amoxicillin-clavulanate, at 82 percent. All *S. aureus* isolates from pigs and dogs were resistant to penicillin (GARP–Tanzania National Working Group 2015).

In India, 100 percent resistance to sulfadiazine was detected in *Pasteurella multocida* isolates in chickens and other fowl, and resistance to amikacin, carbenicillin, erythromycin, and penicillin was also widespread (Shivachandra et al. 2004). Resistance has also been reported in *Staphylococcus* and other bacteria in poultry litter: 75 percent of isolates were resistant to streptomycin, and more than 50 percent were resistant to erythromycin, tobramycin, and ampicillin (Dhanarani et al. 2009).

Effects of animal antibiotic use on human health

What effect does antibiotic use in animals have on the overall burden of antibiotic resistance? Proof that antibiotic use in animals (particularly for growth promotion, and to a lesser extent for prevention) has a significant effect on human health has been elusive but is growing.

Several lines of evidence connect antibiotic use in livestock with effects in humans:

- direct animal-to-human transmission of resistance;
- animal food-to-human transmission of resistance;
- food-borne outbreaks of infection; and
- parallel trends in antibiotic use in animals and related antibiotic resistance in humans.

Because antibiotic resistance is not usually restricted to a single bacterial species, understanding the direct connection between animals and humans is complicated. Various transmissible genetic elements (e.g., plasmids, cassettes) that carry resistance genes may be incorporated by a host of different bacteria. With current technology for genetic analysis, identical elements can be identified regardless of the bacteria in which they are found.

ANIMAL-TO-HUMAN TRANSMISSION OF RESISTANT BACTERIA

The first building block of evidence for effects on human health from antibiotic use in livestock is the finding that

MRSA has been found in 12 percent of animal products—beef, veal, lamb, pork, and a variety of fowl—in Denmark, and in dairy products in Italy.

antibiotic-resistant bacteria are transmitted from animals to their human handlers. Levy et al. (1976) first demonstrated this with a study of chickens and the transmission of intentionally tagged tetracycline-resistant strains of *E. coli* to poultry farm workers, including the farm family. This finding has been corroborated by many cross-sectional studies that demonstrate identical strains of antibiotic-resistant bacteria in farm animals and farm workers (e.g., Zhang et al. 2009). Genetic analysis available in recent years has confirmed the results. A related finding is that workers on farms that use antibiotic growth promoters have higher rates of antibiotic-resistant gut bacteria than workers on farms that do not use them, and than the general public (e.g., Price et al. 2007).

In a review of the connection between antibiotic use in food animals and human health, Marshall and Levy (2011) document the range of animals, bacterial species, and antibiotic resistance profiles that demonstrate animal-to-human spread. In addition to chickens, the animals involved include pigs and cows; in addition to *E. coli*, bacteria include *Salmonella*, *Enterococcus faecalis*, *E. faecium*, and MRSA. Resistance in humans to a range of antibiotics used in animals, including some used only in animals (e.g., apramycin), has been documented.

FOOD-TO-HUMAN TRANSMISSION OF RESISTANT BACTERIA

Evidence that antibiotic-resistant bacteria originating in livestock enter the food chain is abundant. For instance, resistant *E. coli* have been found in beef carcasses that were stored for 24 hours in a cooler and later made into ground beef (Marshall and Levy 2011). MRSA has been found in 12 percent of animal products—beef, veal, lamb, pork, and a variety of fowl—in Denmark, and in dairy products in Italy (de Boer E. et al. 2009; Normanno et al. 2007). People handling these foods before cooking or after inadequate cooking can acquire the resistant (and other) bacteria.

FOOD-BORNE OUTBREAKS OF INFECTION

Large outbreaks of food-borne infections of antibiotic-resistant bacteria have occurred across the globe. An early example is a 1985 outbreak of multidrug-resistant *Salmonella* Typhimurium in the United States, resulting in one death, which was linked to unpasteurized milk (Tacket et al. 1985). In Denmark, an outbreak of nalidixic acid-resistant *S. Typhimurium* in 1998 was linked to pork, and the identical resistance element was found in herds, the slaughterhouse, and the human patients (Molbak et al. 1999).

Similar findings have emerged from all over the world, involving virtually all food animals (including fish) and a host of bacteria, including *E. coli*, *Enterococcus*, *Aeromonas*, and various species of *Salmonella* (Marshall and Levy 2011).

PARALLEL TRENDS IN ANIMAL ANTIBIOTIC USE AND RESISTANT INFECTIONS

A final category of evidence comes from studies of trends in antibiotic use in animals and corresponding trends in antibiotic resistance in animals, humans, and the environment. These studies are difficult to conduct and analyze; however, they have important implications for human health (Marshall and Levy 2011).

In Canada, the third-generation extended-spectrum cephalosporin ceftiofur, member of a class considered critically important by the World Health Organization (WHO), was used at the egg stage of broiler chicken farming, which is not an approved use in Canada. The prevalence of resistant strains of *Salmonella* and *E. coli* in chickens and the same *Salmonella* strains in humans rose through 2005, when ceftiofur use was stopped temporarily. Within one year after the cessation of ceftiofur use, resistance levels in humans and chickens decreased to levels one-half to one-quarter of their highest levels from the previous year. When ceftiofur use resumed, resistance levels again rose (Dutil et al. 2010).

Another example: the United States, Spain, and the Netherlands experienced sharp increases in fluoroquinolone-resistant *Campylobacter* in humans after use of these drugs in poultry began in the 1980s. The frequency increased eight- to 16-fold by the mid-1990s (Endtz et al. 1991; Sánchez et al. 1994; Smith et al. 1999).

Several other cases have been documented in high-income countries, but little is known about similar relationships in LMICs because of the absence of antibiotic resistance surveillance for humans and animals.

REGULATION OF ANTIBIOTICS IN FOOD ANIMALS *Early concerns*

The use of antibiotics to promote growth in farm animals dates to the 1940s and 1950s (Jukes et al. 1950), when it was found that small amounts of the antibiotic aureomycin (chlortetracycline) fed to chickens, pigs, and calves made them grow larger and faster. The drug boosted the animals' efficiency in converting feed into retail meat: a given amount of feed resulted in heavier animals.

As early as the 1960s, concerns were raised about the use of antibiotics in livestock, prompting the U.K. Parliament to appoint a committee to investigate the role antibiotic use in animals played in the rise of antibiotic resistance in humans across the globe. The resulting 1969 Swann Report recommended restrictions, but they were not implemented until more than four decades later. The report proposed restricting antibiotics in animal feed (except by prescription) only to those drugs that had "little or no application as therapeutic agents in man or animals" and would not otherwise promote resistant organisms. The report also recommended that all therapeutic antibiotics in animals be available only with a veterinarian's prescription (Swann et al. 1969).

In the United States, FDA began formally considering the issue in 1970. An FDA task force recommended some restrictions, though not as extensive as those in the Swann Report. Further proposed actions to restrict antibiotic use drew opposition from

the livestock industry, based largely on a lack of direct evidence linking animal antibiotic use to human health problems. However, in the United States and Europe, major reports have been issued regularly from various research and policy bodies (including WHO), reviewing the evidence and refining conclusions (e.g., Pew Commission on Industrial Farm Animal Production 2008).

In a recent report for the Organisation for Economic Co-operation and Development (OECD), CDDEP and Princeton University researchers modeled the effects of eliminating antibiotic use for growth promotion on worldwide meat production and found more modest effects than previously assumed (Laxminarayan et al. 2015) (Box 3-2).

Regulatory and voluntary measures

EUROPEAN UNION

In 1986, Sweden became the first nation to prohibit antibiotic growth promoters in animal feed. The glycopeptide antibiotic avoparcin was banned in Denmark in 1995 and in Germany in 1996 because it was believed to contribute to resistance in humans to vancomycin, a very important last-resort antibiotic (Castanon 2007).

In 1995, Denmark also prohibited veterinarians from selling antibiotics to farmers for a profit (Aarestrup 2012). At the same

time, the Danish government banned the use of virginiamycin and then avoparcin as growth promoters because of worrisome findings of antibiotic resistance that were made public. At least in part because of this publicity, poultry and then pork producers in Denmark voluntarily ceased all antibiotic growth promoter use from 1998 to 2000 (Aarestrup 2012).

The EU followed Sweden and Denmark's lead, and in 2003, an EU regulation declared that most antibiotics would no longer be allowed as feed additives as of January 1, 2006 (European Union 2003). Since then, overall sales of antibiotics for animals have fallen somewhat or remained low in most of Western Europe, where reliable data are available from a surveillance system for antibiotic sales and antibiotic resistance in animals and humans (Figure 3-3). Usage levels vary tremendously, however, indicating the opportunity for further decreases in most countries. The overall decline may mask a trend in increasing therapeutic antibiotic use with the ban on growth promotion. This is illustrated for Denmark in Figure 3-4.

The European countries that have maintained antibiotic use at low levels in animals have continued to work with all parties to address problems as they arise. Several countries have also established surveillance programs similar to Denmark's, which collects data at the population level down to the level

BOX 3-2. PHASING OUT ANTIBIOTIC GROWTH PROMOTION: WHAT EFFECTS?

Antibiotic use for growth promotion is the biggest target for reducing antibiotic use in animals without jeopardizing their health. This use has been or is being phased out in most high-income countries, but not in the rest of the world, where demand for meat is steadily increasing. Will forgoing antibiotics for growth promotion make a material difference in the quantity of meat available or the price to farmers and ultimately consumers?

Laxminarayan and colleagues modeled the potential effects for cattle, poultry, and swine for every country, with assumptions for a high and a low bound for each type of animal, based on high and low estimates of the size of the effect of adding antibiotics for growth promotion. Their research revealed that estimates from earlier studies (the 1980s) were systematically larger than from more recent studies (the 2000s):

SPECIES-SPECIFIC RELATIVE AVERAGE DAILY GROWTH DIFFERENCE BETWEEN ANIMALS RAISED WITH AND WITHOUT ANTIBIOTICS AS GROWTH PROMOTERS		
	1980s literature (%)	2000s literature (%)
Cattle	7	3
Chickens	4	0.7
Pigs	9	1

Source: Laxminarayan et al. (2015)

Using the greater effect sizes from the 1980s literature, the annual global loss in meat production value was projected at \$44.1 billion; using the lesser effect sizes from recent research, the projected loss was \$13.5 billion.

Other researchers have made similar estimates, several for the United States, most suggesting relatively small or negligible effects (e.g., Graham et al. 2007; Sneeringer 2014) and others projecting greater effects, including as much as a 9 percent decrease in net profits to the U.S. swine industry (Miller et al. 2003).

In practice, the effects of eliminating antibiotic growth promotion are likely to vary considerably around the world and within countries, depending on current practices and external conditions (Laxminarayan et al. 2015). Operations with better sanitation, less crowding, and more modern production practices are likely to be affected less than older operations that have not updated their facilities and practices. In Sweden, the ban on growth promoters had a greater effect on producers with lower hygiene standards (Wierup 2001).

Studies in the United States and Europe show that the effects of phasing out antibiotic growth promoters can be minimized by improved livestock management, including vaccination, segregation of herds or flocks by age, optimal sanitation and ventilation systems, better feed, and improved biosecurity. These measures have many other obvious benefits as well. Better management should be the focus of improving livestock production, particularly in LMICs, where increased demand is greatest.

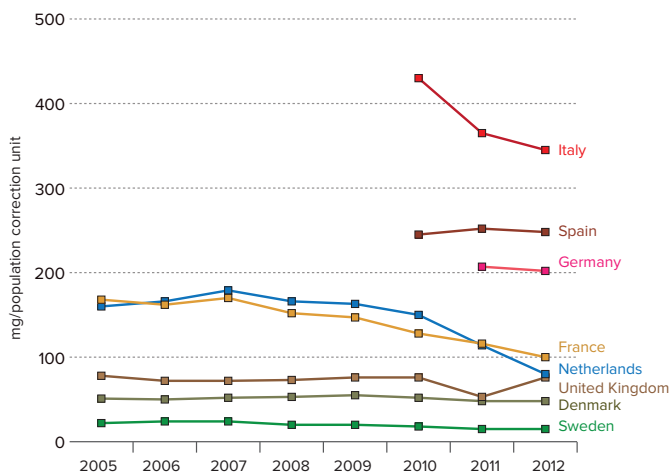


FIGURE 3-3: Sales of active ingredients of antibiotics for food animals in selected European countries, 2005–2012

Source: Elliot 2015

of the individual farm. The need for continued vigilance and information is worth keeping in mind for other countries, particularly LMICs, which have not yet taken concrete steps to minimize antibiotic use in food animals.

UNITED STATES

In 2011 and 2013 in the United States, FDA issued voluntary guidelines for the producers of veterinary drugs that are added to water or feed, with the aim of eliminating the use of medically important antibiotics as growth promoters by the end of 2016 (U. S. FDA 2013). This followed some limited regulations in recent years, such as the prohibition on enrofloxacin use in poultry in 2004 and 2005, and a 2012 ban on off-label use of third- and fourth-generation cephalosporins, both in response to concerns about their effects on human health.

The voluntary guidelines have been met with some skepticism about whether they can succeed absent the force of law. Results will take some years to evaluate, but in the short term the guidance is having an effect. As of June 2014, all 26 drug manufacturers selling a total of 283 products in the United States committed in writing to change their labeling to exclude growth promotion and to require a veterinarian's prescription for these drugs when used therapeutically.¹ As of July 2015, label changes or withdrawals have already occurred for about 40 products.²

OTHER COUNTRIES

In 2014, the Canadian government implemented a voluntary strategy similar to the effort by FDA. Three non-EU members of OECD—Mexico, South Korea, and New Zealand—have all banned the use of antibiotic growth promoters, but the drugs are still authorized in Japan, among other countries. Antibiotic growth promoters are not banned in most of the non-OECD countries that are major meat producers, such as Argentina, Brazil, China, India, Indonesia, Philippines,

¹ <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm403285.htm>

² <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm>

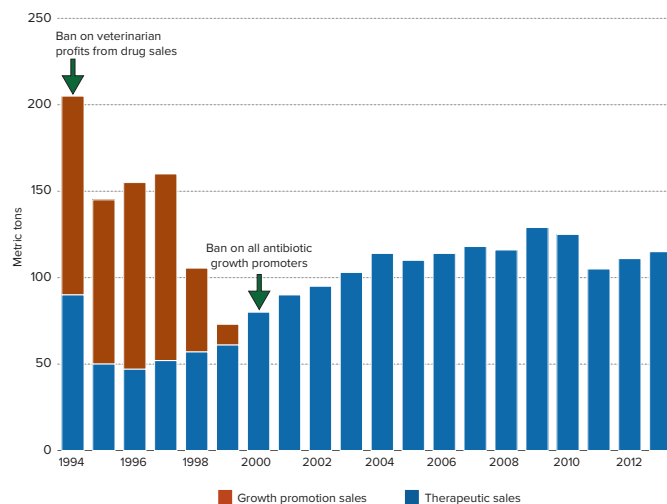


FIGURE 3-4: Sales of active ingredients of antibiotics for food-producing animals in Denmark

Source: DANMAP 2013 (adapted)

Russian Federation, and South Africa (Table 3-2) (Laxminarayan et al. 2015).

ANTIBIOTIC-RESISTANT BACTERIA AND RESISTANCE GENES IN THE ENVIRONMENT

Antibiotic resistance genes, antibiotic-resistant bacteria, and antibiotic residues are found not only in people and animals but throughout the environment. Both antibiotic molecules and antibiotic-resistant organisms occur naturally; what causes concern is the manufactured antibiotics and resistant organisms that find their way from people and animals into the environment.

Antibiotic residues in the environment

Antibiotic residues enter the environment primarily through human and animal waste and from manufacturing (Figure 3-5). After being taken as medication (by humans or animals), antibiotic residues enter the environment when excreted in feces and urine (Daghrir and Drogui 2013). People also flush unused antibiotics down toilets, hospitals improperly dispose of medical wastes, and septic systems leak residues into soil and groundwater.

Once in the environment, these residues may degrade, but some antibiotics survive treatment in water-processing plants (Michael et al. 2013), and residues have been detected in rivers, sediments, and soils (Halling-Sørensen et al. 1998).

Antibiotics in animal feed may seep directly into the soil or pass through animals and be deposited into the soil as waste. A high percentage of antibiotics can pass through animals into the environment: up to 90 percent of an antibiotic dose can be excreted in their urine and up to 75 percent in their feces (Sarmah et al. 2006). From the soil, antibiotics may seep into groundwater and move through the environment. In aquaculture, antibiotics disperse in the water and may be deposited in sediment.

In China, high concentrations of antibiotics have been detected in sediment and water samples, and it has been suggested that fish ponds serve as reservoirs of both antibiotic residues and resistance genes (Xiong et al. 2015).

Antibiotic manufacturing can add locally significant concentrations of antibiotics and other drugs to the environment. Hyderabad, India, an area of intense pharmaceutical manufacturing, has nearly 100 plants that supply drugs to Europe, the United States, and other parts of the world. The wastewater from these plants is processed at a single plant. In 2008, the processed effluent from the treatment plant and water from two nearby lakes and six wells were analyzed (Fick et al. 2009). Researchers found severe contamination in all water sources. In one lake, levels of ciprofloxacin and cetirizine “exceeded human therapeutic blood plasma concentrations.” In addition, the levels of fluoroquinolones in the water sources were found to be 100,000 to 1 million times higher than levels found in surface water contaminated with sewage in the United States and China, and these levels were higher than any ever reported in the literature. The high levels of contamination indicate that the antibiotics in the water sources were very likely mixing with significant bacterial populations, creating a permissive environment for the transfer of antibiotic resistance genes.

Antibiotic-resistant bacteria in the environment

Antibiotic-resistant bacteria occur naturally in the environment: many existed before antibiotics were “discovered” and

A high percentage of antibiotics can pass through animals into the environment: up to 90 percent of an antibiotic dose can be excreted in their urine and up to 75 percent in their feces.

commandeered as medicine. Antibiotic-resistant bacteria have been found in permafrost 30,000 years old, in caves isolated for more than 4 million years (Finley et al. 2013), and in the guts of a previously isolated Amazonian tribe never exposed to drugs (Gibbons 2015). These resistant bacteria may mix with bacteria transmitted through waste in soil and water—considered hotspots for resistance gene transfer—to create new strains. Wildlife may represent another potential reservoir of resistance genes in the environment (Wellington et al. 2013).

Animal waste and manure used as fertilizer can also release resistance genes and resistant bacteria into soil and groundwater (Sarmah et al. 2006). Agricultural use of antibiotics has been connected to resistant bacteria found in surface water in the United States and Mexico, and high rates of antibiotic resistance have been found on farms (Meena et al. 2015).

Antibiotic-resistant bacteria have also been found near wastewater treatment plants and in other water sources worldwide (Meena et al. 2015). In a highly publicized study in New Delhi in 2011, plasmids carrying the resistance element NDM-1 were found in two of 50 drinking water samples and

TABLE 3-2. REGULATION OF ANTIMICROBIAL USE IN LIVESTOCK IN OECD COUNTRIES

OECD country	Legislative status of country in terms of animal use of antibiotics	
	Ban on antibiotic growth promoters	Prescription requirement to use antibiotics in animals
Australia	No, but some AGPs are banned (fluoroquinolones, avoparcin, virginiamycin, etc.) (Australian Commission on safety and quality in health care, 2013).	Nearly all veterinary antibiotics can only be sold on a veterinarian prescription.
Canada	No. The Canadian government issued a notice in April 2014 to stakeholders mimicking the FDA approach to voluntarily phase out use of medically important antibiotics as growth promoters (Government of Canada, 2014).	No. Plan to develop options to strengthen the veterinary oversight of antibiotic use in food animals in line with the FDA approach.
Chile	No data.	No data.
E.U. Member States	Yes. All AGPs banned in 2006 (European Union, 2003).	Yes.
Israel	No data.	No data.
Japan	No (Maron et al., 2013).	Yes.
Mexico	Yes, AGPs were banned in 2007 with some exceptions (avoparcin, vancomycin, bacitracin, tylosin, virginiamycin, etc.) (Maron et al., 2013).	Yes.
New Zealand	Yes, for the critically and highly important antibiotics listed by both WHO and OIE (MAF New Zealand, 2011).	Yes, for antibiotics identified with the potential for resistance problems.
South Korea	Yes, since 2011 AGP use has been discontinued until a veterinary oversight system can be put in place (USDA, 2011).	Yes, the veterinary oversight system is currently being developed.
Turkey	No data.	No data.
United States	No. The FDA released voluntary guidelines for the industry to withdraw the use of medically important antibiotics as growth promoters (U.S. Food and Drug Administration, 2013).	No. Under the new FDA guidance for industry, use of medically important antibiotics will be under the oversight of licensed veterinarians.

Source: Teillant and Laxminarayan (2015)

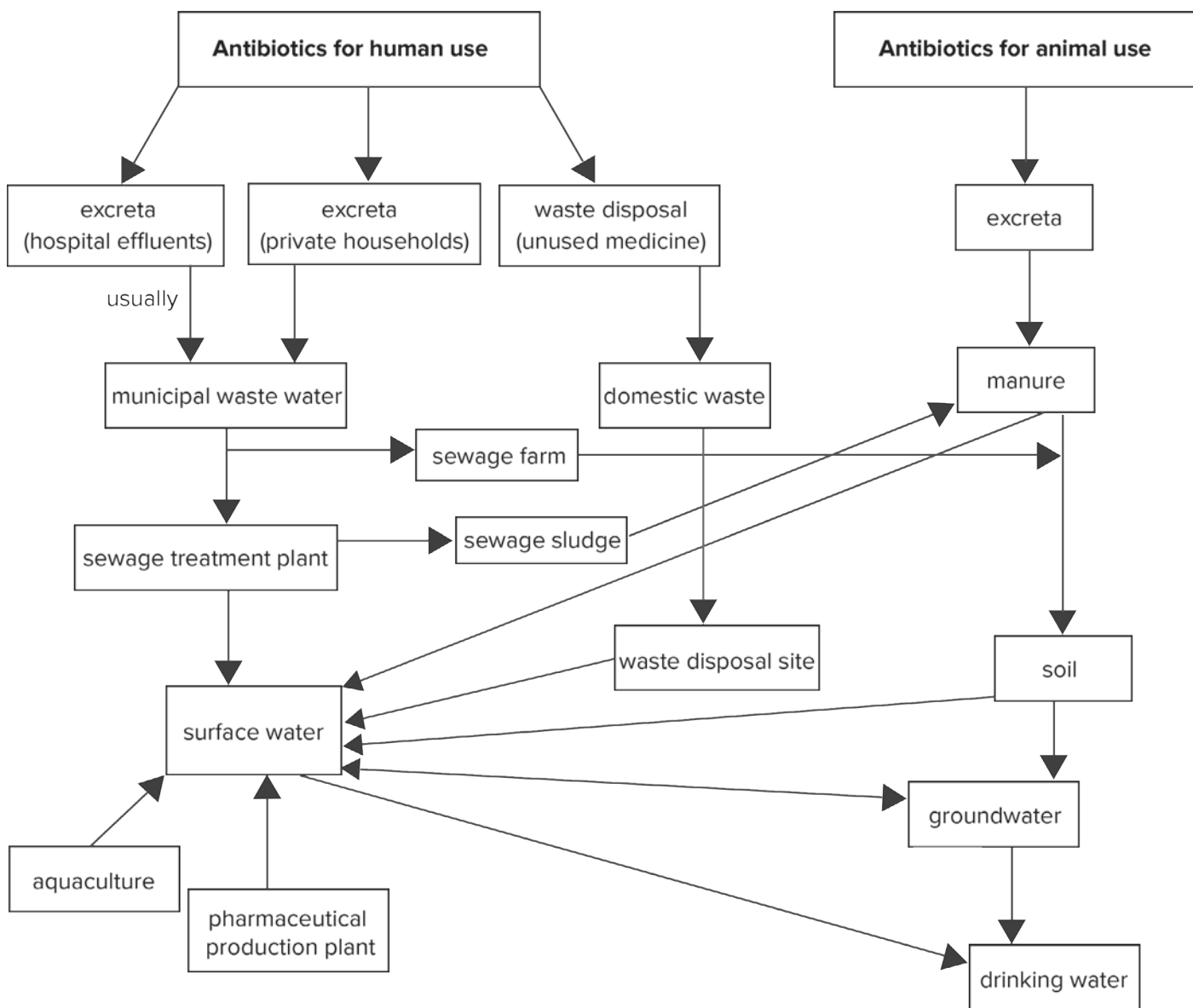


FIGURE 3-5: Sources and pathways for antibiotic contamination of water and soil

Source: Heberer 2002 (adapted)

51 of 171 seepage samples. The bacteria harboring NDM-1 included *Shigella* and *Vibrio cholerae* (Walsh et al. 2011).

Antibiotic-resistant bacteria in the environment may come into contact with humans through contaminated food and water, or by direct human and animal contact. Hotspots include hospitals, wastewater systems, pharmaceutical manufacturing sites, and food animal production sites in agriculture and aquaculture (Berendonk et al. 2015).

Although 2 billion people gained access to improved sanitation between 1990 and 2014, more than one-third of the world’s population—2.5 billion people—still lack access (WHO-UNICEF 2014) (Figure 3-6). Many of these people are living in surroundings contaminated by human and animal waste and are exposed to a high concentration of infectious organisms, including antibiotic-resistant bacteria.

Interventions and regulations

Preventing antibiotic resistance genes from reaching people is the most important goal for human health. The best way

...levels of fluoroquinolones in the water sources were found to be 100,000 to 1 million times higher than levels found in surface water contaminated with sewage in the United States and China...

to achieve this is through improved sanitation, which is a continuing global challenge. Several other approaches can reduce antibiotic contamination from agriculture: managing nutrients, controlling runoff, composting manure, and upgrading infrastructure—all low-cost solutions (Pruden et al. 2013). Managing hotspots by containing industrial and hospital wastes before they reach water sources is also needed. Overall, strengthening control through risk assessment, surveillance, and interventions can reduce the amount of antibiotics entering the environment (Berendonk et al. 2015).

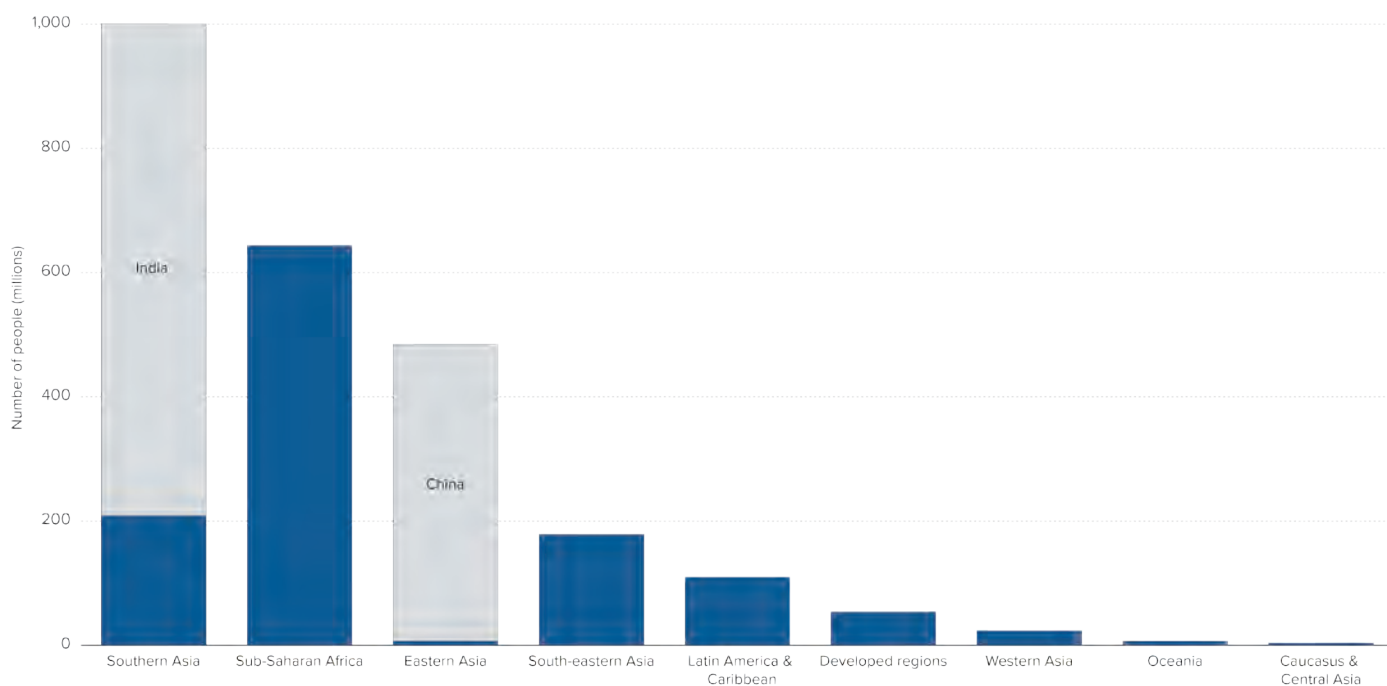


FIGURE 3-6: Population without access to improved sanitation, by MDG region 2012

Source: WHO/UNICEF 2014

Although some legislation addresses antibiotic residues in animal products, no current regulation or international guidelines exist for antibiotic residues in drinking water, despite the detection of high levels of antibiotic residues in various water sources and the known transmission of bacteria through drinking water (Sarmah et al. 2006; Finley et al. 2013). In addition, antibiotic outflows from manufacturing are currently unregulated (Meena et al. 2015).

CONCLUSIONS

Antibiotic use in food animals began almost as early as it did in people and has grown steadily, with little oversight. Today, far more antibiotics are consumed by animals than by people, the vast majority for growth promotion and disease prevention, as a substitute for hygiene and nutrition. The

growing demand for meat and other animal products over the next few decades presages a potentially massive increase in antibiotic use, even greater than the increase in demand as intensive large-scale production replaces small-scale operations in LMICs. Now is the time to make sure that conditions are established to safely eliminate most animal use of antibiotics. This may entail an economic cost but should not harm animal health and is likely to decrease the burden of antibiotic resistance in the human population.

Some of the antibiotics used by people and animals end up in ground and surface water and soil. The consequences of this antibiotic load in the environment are just beginning to be studied. Early research suggests that it adds to the total burden of antibiotic resistance in the world, although effects on humans cannot yet be measured.

KEY MESSAGES

- Antibiotics lose effectiveness over time as antibiotic resistance evolves and spreads. New antibiotics are more expensive and out of reach for many who need them, especially in low- and middle-income countries with a high burden of infectious diseases.
- New agents are not the only, or the most important, tools in maintaining the global stock of antibiotic effectiveness. Conserving the effectiveness of existing antibiotics and complementary technologies are vital.
- An “empty pipeline” argument has dominated the discussion about maintaining antibiotic effectiveness, leading to an emphasis on incentives for new antibiotic development to the exclusion of policies that encourage antibiotic conservation.

New antibiotics are needed to treat the modest but growing burden of multidrug-resistant infections, and a broader array of effective antibiotics will be critical over the coming decades as antibiotic use increases globally, driving resistance. New antibiotics that are more effective, safer, or easier to use will also find a ready market.

Independent analysis of the totality of the evidence confirms that the antibiotic pipeline is reasonably healthy and has been consistently productive for the past three decades (Outterson et al. 2013) without special incentives. This is contrary to widely cited analyses that are based on selected years only (IDSA 2004, Boucher et al. 2013), depicting an almost empty pipeline. In fact, many of the antibiotics developed and approved in recent years did not respond to needs and were withdrawn for lack of market share.

However, new agents are not the only, or necessarily the most important, tools in maintaining the ability to cure infections, particularly in lower-income countries, where their high prices place them out of reach (Kariuki et al. 2015). The conservation measures embodied in antibiotic stewardship can slow and in some cases even reverse the resistance curve, paying greater dividends than new antibiotics do, yet real financial investment in conservation is almost entirely lacking.

This chapter reviews the current universe of antibiotics, the development pipeline, innovation and conservation approaches to sustaining the effectiveness of antibiotics, other approaches to reducing infection, and new technologies that could complement or replace antibiotics.

CURRENT AND FUTURE ANTIBIOTIC SUPPLY

The antibiotic era began in the 1930s, with the discovery and isolation of bactericidal compounds made by soil-dwelling actinomycetes fungi. Over the next few decades, during what has been called the golden era of antibiotic drug discovery, at least 65 antibiotics in nine classes (Table 4-1) were found and introduced into medical use (Lewis 2013). Antibiotic drug discovery progressed from naturally occurring compounds to include two classes of synthetic compounds. Antibiotic research and development today focuses on

Every new generation of new antibiotics has proven exponentially more expensive than its predecessors.

derivatives of older classes of antibiotics and discovery of novel compounds, both synthetic and natural, using innovative discovery platforms (Lewis 2013). Every new generation of new antibiotics has proven exponentially more expensive than its predecessors (Figure 4-1).

The number of new antibiotics in development and emerging from the research and development pipeline has varied over time, as have drugs for most indications. The early years produced the greatest number of antibiotics, a large proportion of which are still on the market and effective against a majority of pathogens. New antibiotics have slowly been added, enlarging the number of classes.

In 2014, seven new antibiotics were approved or introduced for approval worldwide, including two that target complicated urinary tract and intra-abdominal infections, three that target acute bacterial skin and skin structure infections, and four that qualified for fast-track regulatory approval by the U.S. Food and Drug Administration (FDA) (Doshi 2015) (Table 4-2).

In recent years, some older antibiotics that had been largely phased out have been returned to use to treat multidrug-resistant infections, particularly highly resistant Gram-negative infections, for which there are few alternatives.¹ One of the most prominent of these older antibiotics, colistin, was used from the late 1950s into the 1970s, and then rarely used until the 2000s, when it was revived as a last resort for treating multidrug-resistant Gram-negative infections. However, because it was originally tested and approved decades ago, little is known about optimal regimens, including both effectiveness and adverse effects. Toxicity is the main reason it fell out of favor, when seemingly safer aminoglycosides were introduced. A global survey of indications and regimens has found enormous inconsistencies in how and when colistin is used, including ways

¹ Gram-negative bacteria have a thin cell wall that resists the Gram stain and, more importantly, renders them naturally resistant to many antibiotics.

TABLE 4-1. INTRODUCTION OF ANTIBIOTIC CLASSES

Antibiotic class	Year introduced	Target or activity
Sulfa drugs/sulfonamides (synthetic)	1936	Gram-positive
β -lactams (penicillins, cephalosporins, carbapenems, monobactams)	1938	Broad-spectrum
Aminoglycosides	1946	Broad-spectrum
Chloramphenicols	1948	Broad-spectrum
Macrolides	1951	Broad-spectrum
Tetracyclines	1952	Broad-spectrum
Lincosamides	1952	Gram-positive
Rifamycins (ansamycins)	1958	Gram-positive
Glycopeptides	1958	Gram-positive
Quinolones (synthetic)	1968	Broad-spectrum
Streptogramins	1998	Gram-positive
Oxazolidinones (synthetic)	2000	Gram-positive
Lipopetides	2003	Gram-positive
Fidaxomicin	2011	Gram-positive
Diarylquinolines	2013	Narrow-spectrum
Teixobactin	-	Gram-positive

Source: Adapted from Lewis, 2013

that are clearly suboptimal and could promote resistance to it and other polymixins (Wertheim et al. 2013).

The antibiotic pipeline

As of December 2014, at least 37 new antibiotics, developed by 32 mainly small companies, were in the development pipeline for approval in the United States. Eight of these were in Phase 3 (the final stage, involving large-scale clinical trials), and for one, a new drug application had been submitted to FDA for approval (Pew Charitable Trusts 2014). At least two of the drugs in the early phase of development use novel mechanisms to attack bacteria by circumventing bacterial resistance to available antibiotics. Of the drugs, 22 are potentially effective against Gram-negative pathogens (Table 4-3).

In 2015, teixobactin, an antibiotic belonging to a new class, was discovered through the novel growth of uncultured organisms in a laboratory at Northwestern University. Preliminary tests did not reveal any resistance to the compound by *Staphylococcus aureus* or *Mycobacterium tuberculosis*. Teixobactin may prove to be the first antibiotic with the potential to avoid or delay the development of resistance (Ling et al. 2015).

The deficit of greatest concern is a lack of new drugs in the pipeline to treat Gram-negative infections, particularly health-care associated infections, many of which are already resistant to most available agents. These include carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum beta lactamase (ESBL) producers (see

In recent years, some older antibiotics that had been largely phased out have been returned to use to treat multidrug-resistant infections, particularly highly resistant Gram-negative infections, for which there are few alternatives.

Chapter 1 for further discussion). Substandard quality drugs are another, related concern (Box 4-1).

ANTIBIOTIC RESEARCH AND DEVELOPMENT

A great deal has been written about the scientific and financial challenges of developing new antibiotics. The current discussions and initiatives have their roots in *Challenge and Opportunity on the Critical Path to New Medical Products*, a report by the U.S. FDA (2004), and a contemporaneous report, *Bad Bugs, No Drugs*, by the Infectious Diseases Society of America (2004). The most persistent arguments have been in support of government financial and policy changes intended to speed the entry of new antibiotics to the market. The following sections highlight scientific and financial issues in antibiotic research and development.

Scientific challenges

Developing drugs of any kind is challenging. Only a fraction of drugs that begin the development process emerge as effective and safe enough to be approved by a stringent regulatory authority, such as FDA or the European Medicines Agency

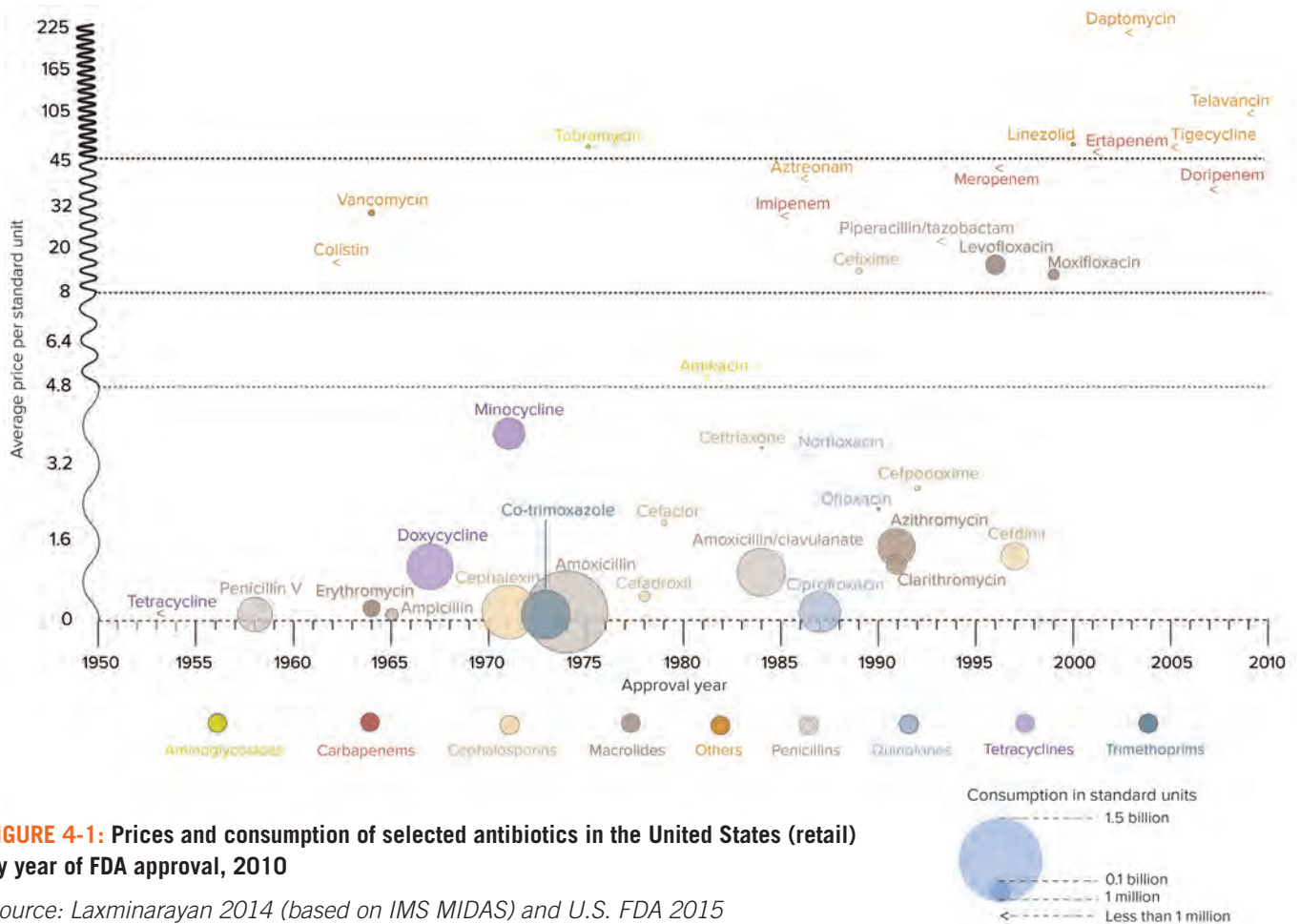


FIGURE 4-1: Prices and consumption of selected antibiotics in the United States (retail) by year of FDA approval, 2010

Source: Laxminarayan 2014 (based on IMS MIDAS) and U.S. FDA 2015

Average price per standard unit is determined by dividing total revenue by sales (retail)

TABLE 4-2. ANTIBIOTICS APPROVED IN 2014			
Antibiotic (trade name)	Company	Drug class	Indications
Ceftobiprole (Zevtera)	Basilea	Cephalosporin	Community- and hospital-acquired pneumonia
Dalbavancin (Xydalba, Dalvance)	Actavis	Lipoglycopeptide	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Oritavancin (Orbactiv)	The Medicine Company	Glycopeptide	Acute bacterial skin and skin structure infections caused by gram-positive bacteria, including MRSA
Tedizolid (Sivextro)	Cubist	Oxazolidinone	Acute bacterial skin and skin structure infections, hospital-acquired bacterial pneumonia
Ceftolozane + tazobactam (Zerbaxa)	Cubist	Novel cephalosporin+beta-lactamase inhibitor	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia
Levofloxacin inhaled Aeroquin, (Quinsair [EU])	Actavis	Fluoroquinolone	Chronic pulmonary infections due to <i>P. aeruginosa</i> in adult patients with cystic fibrosis
Ceftazidime + avibactam (Avycaz)	Actavis	Cephalosporin + beta-lactamase inhibitor	Complicated UTIs and intra-abdominal infections

Source: authors, personal communication (Ursula Theuretzbacher)

MRSA = methicillin-resistant *Staphylococcus aureus*; UTI = urinary tract infection

TABLE 4-3. ANTIBIOTICS IN CLINICAL DEVELOPMENT FOR GRAM-NEGATIVE BACTERIA

Drug	Company	Drug class	Potential indications
<i>Submitted for FDA approval</i>			
Ceftazidime+ Avibactam (CAZ-AVI)	AstraZeneca/Actavis	Cephalosporin + novel beta-lactamase inhibitor	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia
<i>Phase 3</i>			
Carbavance	Rempex Pharmaceuticals	Meropenem + novel boronic beta-lactamase inhibitor	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia, febrile neutropenia, bacteremia, infections caused by CRE
Delafloxacin	Melinta Therapeutics	Fluoroquinolone	Acute bacterial skin and skin structure infections, community- and hospital-acquired bacterial pneumonia, uncomplicated gonorrhea, complicated UTIs and intra-abdominal infections
Eravacycline	Tetraphase Pharmaceuticals	Tetracycline	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia
Plazomicin	Achaogen	Aminoglycoside	Complicated UTIs and intra-abdominal infections, hospital-acquired bacterial pneumonia, hospital-acquired bloodstream infections, infections caused by CRE
Solithromycin	Cempra Inc.	Macrolide	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea, urethritis
<i>Phase 2</i>			
AZD0914	AstraZeneca	DNA gyrase inhibitor	Uncomplicated gonorrhea
S-649266	Shionogi	Cephalosporin	Complicated UTIs
Avarofloxacin	Actavis	Fluoroquinolone	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections
Ceftaroline+ Avibactam	AstraZeneca/Actavis	Cephalosporin + novel beta-lactamase inhibitor	Unavailable
GSK2140944	GlaxoSmithKline	Type 2 topoisomerase inhibitor	Respiratory tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gonorrhea
Lefamulin	Nabriva Therapeutics	Pleuromutilin	Acute bacterial skin and skin structure infections, community and hospital-acquired bacterial pneumonia
Imipenem/ cilastatin+ relebactam	Merck	Carbapenem + novel beta-lactamase inhibitor	Complicated UTIs and intra-abdominal infections, kidney infections, and hospital-acquired bacterial pneumonia
Nemonoxacin	TaiGen Biotechnology	Quinolone	Community-acquired bacterial pneumonia, diabetic foot infection, acute bacterial skin and skin structure infections
Omadacycline	Paratek Pharmaceuticals	Tetracycline	Complicated UTIs, community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections

TABLE 4-3. ANTIBIOTICS IN CLINICAL DEVELOPMENT FOR GRAM-NEGATIVE BACTERIA, *continued*

Drug	Company	Drug class	Potential indications
Radezolid	Melinta Therapeutics	Oxazolidinone	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections
Zabofloxacin	Dong Wha Pharmaceutical	Fluoroquinolone	Community-acquired bacterial pneumonia
POL7080	Polyphor	Macrocyclic LptD inhibitor	Hospital-acquired bacterial pneumonia caused by <i>P. aeruginosa</i> , lower RTIs, bronchiectasis
Finafloxacin	MerLion Pharmaceuticals	Fluoroquinolone	Complicated UTIs and intra-abdominal infections, kidney infection, acute bacterial skin and skin structure infections
Phase 1			
BAL30072	Basilea Pharmaceutica	Monosulfactam	Unavailable
OP0595	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc.	Beta-lactamase inhibitor	Unavailable
Aztreonam+ Avibactam	AstraZeneca/Actavis	Monobactam + novel beta-lactamase inhibitor	Unavailable

Source: Adapted from Pew Charitable Trusts (<http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>).

CRE = carbapenem-resistant Enterobacteriaceae; RTI = respiratory tract infection; UTI = urinary tract infection

(Krans 2014). About 30 percent of drugs that have progressed through animal testing to human testing make it past the first phase of human testing, and about 8 percent are eventually approved. The process can take 13 years once a drug enters Phase 1 trials in humans (Table 4-4) (Independent Institute, 2015). For antibiotics, that portion of the timeline has been shorter, on the order of six to seven years (U.S. FDA 2004).

In the United States, the number of applications and approvals of all new drugs, biologic licenses, and innovative medical devices has been declining since at least 2000 (U.S. FDA 2004; IDSA 2004). Antibiotics are no more affected than other types of drug. The overall decline is attributed in part to increased costs and inefficiencies in the drug development process. Clinical trials for antibiotics are reported to be particularly expensive because of testing against multiple

pathogens and indications, or against rare multidrug-resistant infections, which bring recruitment and diagnostic difficulties.

For antibiotics, the biggest challenge is discovering entirely new classes, particularly with narrow spectrums of activity. Historically, it has been easier to find new members of existing classes, and progress is made when these new members are better in some way than the originators. However, new entrants are at risk of loss of effectiveness due to resistance that has already developed to earlier entrants. Cross-resistance within antibiotic classes is common (Mossialos et al. 2010). Over time, it also becomes harder to find new agents in established classes.

Financial issues

The argument is often made that antibiotics offer a poorer return on investment than other types of drugs (Spellberg 2012), for

TABLE 4-4. OVERVIEW OF FDA DRUG DEVELOPMENT PROCESS

Phase	Timeline	Overall probability of success
Preclinical	1–6 years	
Clinical	6–11 years	
Investigational new drug application		
Phase 1	21.6 months	30%
Phase 2	25.7 months	14%
Phase 3	30.5 months	9%
Approval of new drug application	0.6–2 years	8%
Phase 4, post-market surveillance	11–14 years	

Source: http://www.fda.gov/oc/ohrt/2012/08/20120801_ohrt_approval_process.html

BOX 4-1. ANTIBIOTIC QUALITY ISSUES

Antibiotics (and other drugs) are “substandard” if they do not contain what the label states, either qualitatively (the active ingredients are missing or different) or quantitatively (the amounts, allowing for an accepted margin of error, are incorrect). The production of substandard antibiotics may be unintentional, resulting from poor manufacturing practice, or the drugs may be deliberately counterfeited and sold solely for profit.

Substandard manufacturing

Poorly manufactured drugs may enter the market because of insufficient quality control and a lack of necessary microbiological technologies for testing. Even antibiotics that were manufactured to specifications may degrade before they reach consumers because of hot climates, bottlenecks and delays in supply chains, poor storage conditions, and weak distribution systems. Ideally, drugs would be tested throughout this process to ensure quality is maintained, but in reality, such monitoring rarely takes place.

Counterfeit drugs

Counterfeit medicines may enter the market as a result of crime, corruption, and consumers’ reliance on informal drug sellers. It has been estimated that sales of falsified medicines are worth more than \$75 billion (Nayyar et al. 2015). The World Health Organization (WHO) and FDA have estimated that up to 10 percent of drugs worldwide—perhaps even 30 percent in some low- and middle-income countries (LMICs)—may be counterfeit. In Africa and Asia, up to 60 percent of antimicrobials may be falsified, a number that increased 10-fold in the decade from 2002 to 2012. In Europe, an increase has also been detected, but counterfeit drugs make up less than 1 percent of the market in high-income countries (Kelesidis and Falagas 2015; Nayyar et al. 2015).

In LMICs, unlicensed drug sellers contribute to a large portion of substandard drugs sold (Almuzaini et al. 2013). Online sales of medications all over the world may be another opportunity for the distribution of substandard drugs, but this has not been well investigated.

Degraded drugs

At the end user level, antibiotics may degrade because of poor storage conditions or because the products have outlived their shelf life. Substandard products that have too little active antibiotic can boost resistant bacteria, and more

importantly for the patient, may lead to treatment failure and even death. Substandard medicines can also trigger use of higher doses of antibiotics in a subsequent course, on the assumption that the lower dose failed. Broader consequences include a loss of faith in medicines and increased healthcare costs to individuals and governments (Kelesidis et al. 2007).

Studies of antibiotic quality are limited, but low-quality drugs have been identified as a serious issue worldwide, especially in LMICs. What studies have been done have identified an increasing prevalence of substandard drugs in those countries (Tadeg and Berhane 2014; Nayyar et al. 2015). Counterfeit drugs are widely considered to increase rates of drug resistance, though no studies have specifically investigated this correlation for antibiotics (Kelesidis et al. 2007; Newton et al. 2006).

Several large studies have analyzed the quality of antimalarial drugs. A recent estimate laid blame for more than 122,000 deaths in children under age five in 39 countries in sub-Saharan Africa in 2013 on low-quality antimalarials, accounting for 4 percent of under-five deaths in that region (Renschler et al. 2015).

Interventions to reduce substandard drugs

Guidelines for substandard drugs have been produced by WHO, which also runs an International Medical Products Anti-Counterfeiting Taskforce, and the European Union, United Nations, and United States run similar programs at the regional and national level. FDA uses a regulation known as Current Good Manufacturing Practice to ensure drug quality, and the U.S. Pharmacopeial Convention provides reference standards for medications. Few LMICs have any such national program. The U.S. Agency for International Development has funded the Medicines Quality Database, an online tool that can be used to track drug quality in Africa, Asia, and Latin America.

New, collaborative approaches, including a global convention and the development of global standards and national laws, have been suggested (Nayyar et al. 2015). Other experts have recommended stiffer punishments for counterfeit drug producers and stricter enforcement of current laws (Buckley et al. 2013). Developing better, simpler, and more accessible testing methods for substandard drugs could bolster both surveillance and control efforts.

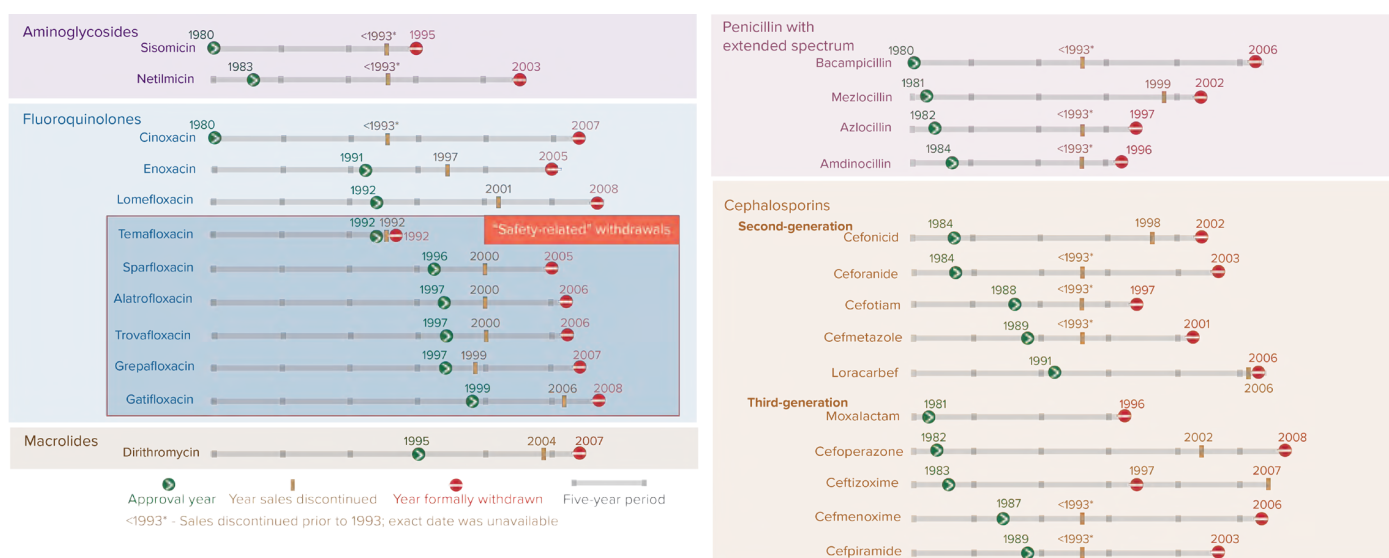


FIGURE 4-2: New antibiotics approved by the U.S. FDA but subsequently withdrawn or discontinued, 1980–2009

Source: *Otterson et al. 2013*

two main reasons. First, antibiotics are taken for a relatively short time, unlike drugs for chronic conditions, such as high cholesterol or hypertension—therapies that many patients start in middle age and continue for decades (Mossialos et al. 2010). Second, prices for new antibiotics are set lower than for other new drugs. However, antibiotics are still very profitable. In 2004, they were the third highest earning drug class behind central nervous system and cardiovascular drugs, bringing in \$26 billion to \$45 billion per year (Powers 2004). Despite shorter courses, many more people take antibiotics than they do other types of drug, and antibiotics can even become “blockbusters.” The combination of amoxicillin and clavulanic acid (marketed in different countries as Augmentin, Amoxiclav, and other trade names) had global sales of \$2 billion in 2001 (www.forbes.com/2002/04/16/0416drugkids.html).

The pharmaceutical industry as a whole is continually evolving. Over the past several decades, the priorities of large multinational companies have changed, and many small biotechnology and pharmaceutical companies have entered the market. Overall, large companies have withdrawn from the antibiotic market or scaled back their efforts. Some small companies now specialize in antibiotic development. The changes have been driven in large part by business considerations, including potentially greater revenues for large companies in other areas of medicine (Fox 2003).

Market approvals and withdrawals

The analysis of antibiotic approvals and withdrawals tells a more nuanced story about research and development than the generalizations about scientific and financial challenges that have been used in arguments to support incentives (Otterson et al. 2013) (Figure 4-2).

In the 1980s, 29 systemic antibiotics were approved by FDA, representing 16 percent of all drug approvals in that decade; in the 1990s, 23 were approved representing 15 percent of approvals; and from 2000 to 2009, nine new antibiotics were approved, representing 11 percent of all approvals during

that time. Of these 61 antibiotics, 26 had been withdrawn from the market by 2013, only six of them required by FDA for safety reasons. The rest were withdrawn voluntarily, and according to industry sales data, few were commercially successful. Manufacturers do not routinely disclose their reasons for voluntarily withdrawing products, however, so precise explanations are not available.

A higher percentage of antibiotics (43 percent of those approved) were withdrawn than other types of drugs approved during that period (13 percent overall). Most were members of two antibiotic classes with many other effective agents (at least some of them generics), the cephalosporins and the fluoroquinolones. None appeared to be withdrawn for reasons of high resistance rates among target organisms.

Sales data suggest that only three of the withdrawn products were commercial successes, suggesting that most were of no greater than modest clinical importance. Supporting this interpretation is the fact that only two of the withdrawn products had been granted FDA’s priority review status (recognizing high clinical value) during their approval phase.

If the call for more new antibiotics is so insistent, why did so many of the approved antibiotics not achieve clinical and commercial success? Most of the new antibiotics were similar to antibiotics that were already available and still effective in their respective classes, and there was little reason to use a new and invariably more expensive product. Commercially successful antibiotics filled unmet medical needs or had other advantages, such as easier dosage regimens or fewer side effects.

Without more detailed information from the companies that developed and withdrew these products, it is not possible to tell a full story. We can conclude, however, that over the past several decades and continuing today, it is not new products are not lacking but rather, antibiotics that address unmet needs. The market does not support antibiotics similar to those available already, at lower prices.

POLICIES FOR ANTIBIOTIC INNOVATION AND CONSERVATION

The arguments in support of promoting antibiotic research and development have led governments to offer incentives and policy analysts to propose interventions, including new business models; strengthened collaboration among industry, academia, and government institutions; and financial inducements. Meanwhile, investments in slowing the evolution and spread of antibiotic resistance are paltry and incentives to encourage conservation are largely nonexistent. In purely economic terms, if the cost of bringing a new antibiotic to market is \$1 billion or more, not including the cost of incentives, then delaying the need for one new antibiotic is worth a conservative \$60 million per year (Laxminarayan 2014). Yet in recent years, the U.S. Centers for Disease Control and Prevention has spent only about \$5 million per year on antibiotic conservation (Laxminarayan 2014).

Three main arguments are used to support the need for innovation incentives:

1. Introductions of new antibiotics have slowed to a trickle, and the pipeline is empty.
As discussed earlier in this chapter, this argument does not seem to represent the current situation. Several new antibiotics have been introduced in each of the past few years, and a reasonable number of drugs are in late-stage development. Although more narrow-spectrum agents and new antibiotic classes are needed in the long term, the pipeline may already be flowing again, with two new antibiotic classes introduced during the past decade and with antibiotics specifically for methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections an increasing public health priority.
2. Antibiotics are less profitable than drugs for other conditions.
Antibiotics are less profitable than some other classes, but are still highly remunerative, as discussed earlier. Even if not attractive enough to large pharmaceutical companies, the anti-infective field has drawn many new small pharmaceutical and biotechnology firms, for whom the scale of profits is rewarding.
3. New antibiotics are kept in reserve for resistant infections.
This hypothetical argument has little evidence behind it. A more likely explanation for why new antibiotics are not widely used is that older, much less expensive antibiotics are effective against most infections. Most antibiotics are approved on the basis of being “non-inferior” to the best available alternative. When products are *more* effective—take the case of voriconazole, an antifungal therapy that is superior to other treatments—they are quickly adopted and widely used, even at prices higher than for the next best agent.

Regardless of the merits of those arguments, governments in the United States and Europe have responded with a number of policies.

...investments in slowing the evolution and spread of antibiotic resistance are paltry and incentives to encourage conservation are largely nonexistent.

U.S. actions to promote new antibiotic development

In the United States, the Generating Antibiotic Incentives Now (GAIN) Act of 2012 extends for five years the period in which companies can sell antibiotics for severe conditions without generic competition. Of the 37 antibiotics under development in December 2014, at least 24 could qualify for GAIN’s exclusivity extension (Pew Charitable Trusts 2014).

A long-standing example (not specific to antibiotics) is the 1983 Orphan Drug Act, which extends tax credits during development and guarantees seven years of market exclusivity to developers of drugs for rare conditions (those affecting fewer than 200,000 patients per year in the United States). An extension of the Orphan Drug Act could be used to cover novel antibiotics or those used specifically for multidrug-resistant infections (Laxminarayan and Powers 2011).

A new wave of proposals is now being considered. In January 2015, the Promise for Antibiotics and Therapeutics for Health (PATH) Act was introduced in the U.S. Congress. The bill would encourage development of new antibiotics that target “unmet medical needs” in specific patient populations. PATH would modify the FDA approval requirements for these specific drugs to make approval easier (Doshi 2015). The bill has substantial support from such organizations as the Infectious Diseases Society of America, the Pew Charitable Trusts, and the Science in Service to Humanity Foundation. Critics have voiced concern that it could have serious consequences for patients’ safety and that drugs would be approved with relatively little information on use in broader patient populations, even though physicians could use them more broadly (Doshi 2015). The bill has not yet been voted on and will remain active throughout the 114th congressional session, which extends through 2016.

Similarly, the 21st Century Cures Act, passed by the U.S. House of Representatives in July 2015, calls for higher reimbursement rates for new antibiotics for Medicare and Medicaid patients, and it loosens the approval requirements for antibiotics (among many other provisions). Increasing reimbursement without any other controls is likely to lead to overuse of these products, and the reduced approval requirements are likely to put patients at risk.

In March 2015, President Obama released the National Action Plan for Combating Antibiotic-Resistant Bacteria (White House 2015), which addresses policy recommendations made by the President’s Council of Advisors on Science and Technology in 2014 (PCAST 2014). One of the five stated goals of the action plan is to “accelerate basic and applied research and development for new antibiotics, other therapeutics and vaccines.” The activities corresponding to this goal are as follows (White House 2015):

1. Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic resistance and the spread of resistance genes that are common to animals and humans.
2. Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
3. Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
4. Develop nontraditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
5. Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.

Like the pending bills in Congress, this plan gives much more weight (and resources) to incentivizing new antibiotic development than it does to conserving the effectiveness of existing and new agents.

European Union action plan

The EU is following similar dictates as the United States. Its New Drugs for Bad Bugs (ND4BB) program was created in response to the Action Plan against the Rising Threats from Antimicrobial Resistance (European Commission 2011), which called for “collaborative research and development efforts to bring new antibiotics to patients.” Under the banner of the Innovative Medicines Initiative, ND4BB will address the spectrum of biological and economic issues. The collaborators are from the pharmaceutical industry, academia, and biotechnology organizations.

ND4BB consists of six projects, the first of which launched in 2013:

1. COMBACTE is creating a pan-European network of excellence in clinical investigation sites, where studies of new agents can be conducted, particularly against multidrug-resistant pathogens. A laboratory surveillance network supports the network. Another aim is to advance the field of clinical trial design for antibiotics.
2. TRANSLOCATION is intended to identify new approaches to preventing resistance arising to antibiotics. The project intends to provide guidance for antibiotic developers, specifying the properties that will make new agents more likely to maintain their effectiveness.
3. ENABLE offers small companies and academic researchers a platform to develop their promising molecular leads into candidate drugs for further testing. The emphasis will be on molecules with promise against Gram-negative infections.
4. DRIVE-AB will develop new economic models to incentivize investment by companies of all types in antibiotic research and development. One goal is to ensure that antibiotics produced through these new models are not oversold or overused, with the intention of prolonging their effectiveness.

Vaccines against pneumococcal pneumonia and rotavirus could reduce antibiotic use and lead to a healthier population.

5. COMBACTE-CARE takes on the challenge of new approaches to treating carbapenem-resistant infections, considered among the most challenging and dangerous types of infection. Novel products and combinations will be studied.
6. COMBACTE-MAGNET aims to find better ways to prevent and treat healthcare-associated infections. It focuses on Gram-negative pathogens, with special attention to intensive care units. A network for surveillance, EPI-Net, has also been established.

CONSERVING AND RESTORING ANTIBIOTIC EFFECTIVENESS

Antibiotic conservation involves both reducing the need for antibiotics and reducing inappropriate and unnecessary use. The interventions mentioned briefly below are discussed in detail in Chapter 5.

Reducing antibiotic demand

Reducing the burden of infectious disease through vaccination, improved water and sanitation, and a food supply free from bacterial pathogens reduces the need for antibiotics. Vaccination adoption and coverage have been improving globally. Vaccines against pneumococcal pneumonia and rotavirus could reduce antibiotic use and lead to a healthier population. Fewer cases of pneumococcal disease directly reduces antibiotic demand and fewer diarrheal cases will reduce the widespread inappropriate use of antibiotics (Chapter 5). Both vaccines fit into existing World Health Organization Expanded Programme on Immunization (EPI) schedules and thus entail only minor programmatic costs. There also are underused vaccines for food animals that would reduce antibiotic demand in the veterinary sector, especially in LMICs.

Reducing inappropriate and unnecessary antibiotic use

Antibiotic stewardship is the broad term for reducing the inappropriate and unnecessary use of antibiotics (Chapter 5). It encompasses both animal and human use and use in the community and in hospitals. Stewardship is often more narrowly identified with hospital practices, especially hand hygiene, infection control and prevention, checklists, and active participation by hospital staff and pharmacists.

ALTERNATIVE AND COMPLEMENTARY APPROACHES

One alternative to developing new antibiotics is finding agents that renew the utility of the antibiotics currently in use. Another is to use inhibitors that are co-administered with antibiotics to neutralize the resistance mechanism of the bacteria and reduce the likelihood that a single set of mutations can develop resistance to drugs simultaneously (Laxminarayan and Powers 2011; Wright 2000). Inhibitors could be used even after the emergence of resistance (Wright 2000).

New products are not the only approach to maintaining antibiotic effectiveness. Antibiotic cycling—using antibiotics for defined periods, withdrawing them, and reintroducing them later—may work in some instances. The assumption is that resistance mechanisms have “fitness costs,” and that without selection, sensitive strains will outcompete resistant strains. The idea of fitness costs is attractive and may apply in some cases, but for some strains of resistant bacteria there may be a fitness advantage rather than a cost (Avison 2005). In England, for instance, sulfonamide resistance levels in *E. coli* did not fall even after a decade-long discontinuation of sulfonamides (Avison 2005).

Improved diagnostic tools

Healthcare providers need rapid diagnostic tests that can distinguish between bacterial and viral infections, between bacterial infections that require treatment with antibiotics and those that do not, and between bacteria with susceptible and resistant strains to certain antibiotics. Such tests would have the potential to improve both antibiotic prescribing and patient outcomes (Antimicrobial Resistance Working Group 2013; Spellberg et al. 2011). The tests would ideally be sensitive, specific, rapid, inexpensive, and usable without sophisticated machinery. That ideal is still a long way off, however.

Rapid diagnostic tests (RDTs) have been developed for some febrile illnesses in the past 20 years. The best known and most widely used are RDTs to detect malaria infection. Ironically, the success of malaria RDTs has probably increased the inappropriate use of antibiotics by healthcare providers. Before RDTs became widely available in the mid-2000s, most fevers in malaria-endemic areas were treated presumptively as malaria. Because most fevers are self-limited, most patients recovered. Those who did have malaria were appropriately treated, even though antimalarials were overused. With RDTs, it is clear that many fevers are not malaria, but it remains difficult to diagnose the true cause. In the absence of malaria, the default treatment is an antibiotic (Baiden et al. 2011). RDTs were a clear advance for malaria and demonstrated the need for other diagnostics. So far, this need has not been met, although some research and development is in progress.

At least 11 RDTs were developed and tested for dengue between 2009 and 2011 and six for enteric fever from 2001 to 2011. Specialized tests have also been designed for leptospirosis, brucellosis, human African trypanosomiasis, visceral leishmaniasis, and rickettsial diseases (Chappuis et al. 2013). Several of these diagnostics have been commercialized, but none have been widely distributed. At an earlier stage of research are biomarkers associated with infection (e.g., procalcitonin and C-reactive protein), which continue to be studied as possible indicators of the need for antibiotics.

The 2014 Longitude Prize, a British award of £10 million, will be awarded for the invention of a diagnostic within five years with the potential to reduce unnecessary antibiotic use.

Factors such as cost, scalability, ease of use, and speed of result will be considered.

Vaccines

Vaccines that prevent bacterial infections directly reduce the need for antibiotics. *Streptococcus pneumoniae* vaccination of infants has greatly reduced the incidence of pneumococcal disease overall, including infection with main antibiotic-resistant strains, which are included in the vaccine used in the United States. This vaccine has reduced antibiotic use and antibiotic resistance directly (Dagan and Klugman 2008). Vaccines that reduce antibiotic use for sensitive pathogens also may have indirect effects in reducing antibiotic resistance, simply by reducing drug pressure on bacteria. Even vaccines that prevent viral diseases can reduce antibiotic use, in two ways. First, they can eliminate many cases of viral disease that would be inappropriately treated with antibiotics. A good example is rotavirus vaccine to prevent diarrhea in children. Second, bacterial infections are common sequelae of some viral diseases. Many deaths from initial influenza infections are caused by secondary bacterial lung infections (McCullers 2014).

The vaccines in widespread use today are true public health interventions, intended to reduce overall morbidity and mortality; the reductions in antibiotic use and resistance are side benefits. However, antibiotic resistance is now playing a role in vaccine development priorities. No vaccine against *S. aureus*, the leading cause of skin and soft-tissue infection and one of the most important healthcare-associated infections (including surgical site and bloodstream infections), has yet been commercialized despite substantial development efforts. Many candidate vaccines have failed, but efforts continue, in large part because MRSA infections are becoming ever more difficult and expensive to treat. A recent candidate called NDV-3 (also potentially protective against the common fungal pathogen *Candida albicans*) has been successful in mice and in early-phase human trials (Yeaman et al. 2014).

Clostridium difficile is another potential vaccine target, as are several Gram-negative organisms. Vaccines for these organisms must take account of the patient populations, which are often older and/or have weakened immune systems (and thus the response to a vaccine may not be robust). Moreover, the vaccine targets may include toxins and virulence factors in addition to the DNA products of the host bacteria. It may also be difficult to develop vaccines that confer long-term immunity, making it challenging to decide whom and when to vaccinate. Despite the challenges, however, eventually some vaccines may be developed that target antibiotic-resistant organisms.

Among the important Gram-negative bacteria, vaccine development is promising for enterotoxigenic *E. coli* (ETEC), *Shigella*, and *Campylobacter*. At least three ETEC vaccines, which are targeted at travelers, are being tested in human trials.² Several *Shigella* and *Campylobacter* vaccines are in similar phases of development.³

² (<http://techlinkcenter.org/summaries/vaccine-human-enterotoxigenic-escherichia-coli-etec/>) (<http://www.path.org/publications/files/VAC-etec-investment-rpt.pdf>)

³ (<http://www.nih.gov/news/health/feb2013/niad-20.htm>) (<http://sites.path.org/vaccinedevelopment/diarrhea-rotavirus-shigella-etec/shigella-and-etec-vaccine-development/>) (<http://www.foodsafetynews.com/2014/05/campylobacter-vaccine-in-human-trials/#.VX8K91VWhBc>)

A vaccine to prevent gonorrhea is also in development, still in the preclinical animal testing phase.⁴

Among the largely hospital-acquired infections, the most promising vaccine candidate is for *Pseudomonas aeruginosa*.⁵ The vaccine has been developed by Valneva, a European biotechnology company, and Novartis and is entering a Phase 2/3 efficacy trial of ventilated patients in intensive-care units.

Extensive efforts to develop vaccines against *Acinetobacter baumannii*⁶ and *Klebsiella pneumoniae*⁷ have thus far been disappointing. These pathogens are such important healthcare-associated pathogens, often highly antibiotic resistant, that work will undoubtedly continue on vaccines to prevent them.

Bacteriophages

Bacteriophages, parasitic viruses of bacteria, are the most abundant organisms on earth. The “phages” of medical interest are those that kill their bacterial hosts. They were discovered in the early 20th century, before the discovery of penicillin. Interest in phages has continued in Eastern Europe at a low level since that time, but their development halted in the West largely because of the success of antibiotics. Today, a few research teams and companies in the United States and Europe are active in research and development of phage products for treating antibiotic-resistant infections (including MRSA) and some Gram-negative infections (*E. coli*, *P. aeruginosa*, *A. baumannii*, *C. difficile*). Among the approved products is SalmoFresh, marketed by Intralytix, a U.S.-based company; a six-phage “cocktail,” it is applied directly to both animal and plant foods to protect against contamination by *Salmonella*. No phage therapies are currently in human use, but some are in clinical trials. For example, a Phase 1/2 trial of two phage cocktails for burns infected with *E. coli* or *P. aeruginosa* is under way in France, Belgium, and Switzerland, funded by the European Union (Gabard and Jault 2015).

Phages could also be used in livestock for disease prevention and treatment, in diagnostics, and in infection control and disinfection in hospitals and other sites. They may also be combined with antibiotics to improve effectiveness and to overcome antibiotic resistance.

Phage products face many challenges, however. For greatest effectiveness, cocktails may need to be altered frequently, with the addition and subtraction of specific phages. The regulatory regimes for drug approval have not been developed to accommodate such products. Phages deserve greater support or at least a fresh appraisal, given the seriousness of antibiotic resistance and the need for new approaches.

CONCLUSIONS

Contrary to a view that predominates in policy discussions, the antibiotic pipeline is healthy and continually producing antibiotics in the absence of incentives to encourage development. Although incentives are not needed to increase the number of antibiotics, there is a role for public policy interventions, including incentives, to ensure that important new antibiotics are affordable, including in lower-income countries. Their availability only in high-income countries will not help the global response.

Insufficient attention has been paid to developing incentives to conserve the effectiveness of the existing universe of antibiotics. What is needed is a balanced set of incentives for both innovation and conservation.

Other approaches to infection control and treatment will also help maintain the effectiveness of current and emerging antibiotics. These include vaccines (for both humans and animals), diagnostic technologies, and complementary and alternative technologies, such as bacteriophages.

⁴ (<http://www.sci-news.com/medicine/science-live-vaccine-gonorrhea-01395.html> and <http://www.sciencedaily.com/releases/2013/09/130918101956.htm>)

⁵ (<http://www.valneva.com/?page=83>) (http://www.drugs.com/clinical_trials/valneva-provides-update-pseudomonas-aeruginosa-vaccine-candidate-16265.html).

⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21044668>

⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22100884>

KEY MESSAGES

- Antibiotic resistance is a global problem, but the solutions are at the national and regional level. The benefits of conservation efforts accrue locally while contributing to antibiotic effectiveness at the global scale.
- Antibiotic use can be rationalized by reducing the need for antibiotics through better public health, by curbing unnecessary use, and by improving access where use is warranted.
- National strategies to change antibiotic use norms should be built around effective interventions that address incentives for conservation in hospital and community settings and in the agricultural sector. Solutions should target both healthcare providers and the public.

CHANGING NORMS ON ANTIBIOTIC USE

Antibiotic resistance has not been a priority on the global health agenda until recently, and a result, many countries—mostly low- and middle-income countries (LMICs)—have not yet developed national strategies to address it. The Center for Disease Dynamics, Economics & Policy (CDDEP), through its Global Antibiotic Resistance Partnership (GARP), has enabled eight LMICs to assess their antibiotic resistance situation and begin developing and implementing strategic responses.

Challenges to implementing such responses vary regionally, and policy solutions must be localized and context specific. Disincentives to antibiotic conservation, such as antibiotic sales that profit doctors or hospitals, should be recognized and modified, a process now playing out in China (Box 5-1).

Funding to develop and implement programs is not the only factor that hinders national strategies to slow antibiotic resistance while improving access for those who need antibiotic drugs. Expertise in infection control, surveillance, microbiology, and antimicrobial stewardship is equally important. Poor laboratory or point-of-care diagnostic services impede good surveillance, appropriate prescribing, de-escalation, and alternative therapy interventions. Poor health infrastructure, including inaccessibility of primary-care services and the difficulty of enforcing limits on antibiotics (e.g., prescription-only laws), are additional obstacles.

Changing social norms about how and when to use antibiotics is central to preserving antibiotic effectiveness in all countries, rich or poor. Antibiotic use must shift from being considered the default treatment to being seen as an exhaustible medical tool to be used when appropriate. Both patients and healthcare providers must be engaged for this change to take place. Although such a change may seem like a high hurdle, health-related social norms are not immutable: consider that smoking was once ubiquitous in public places but is now routinely banned and socially unacceptable in many countries. To support behavior change efforts, incentives affecting antibiotic use should be realigned to discourage overuse and encourage rational use and conservation.

NATIONAL POLICIES TO CHANGE THE NORMS OF ANTIBIOTIC USE

Six strategies contribute to successful national policies for antibiotic resistance and access (Figure 5-1).

1. Reduce the need for antibiotics through improved water, sanitation, and immunization.

The most attractive strategy is to reduce the need for antibiotics by reducing the burden of infectious diseases requiring antibiotics. This can be achieved by improving vaccination coverage (Okeke et al. 1999; Zhou et al. 2008), improving access to clean water and sewerage systems (Cairncross et al. 2010), and ensuring a safe and healthful food supply (Katona and Katona-Apte 2008). Because most antibiotics are used to

BOX 5-1. POLICY CHANGE FOR ANTIBIOTIC STEWARDSHIP IN CHINA

China has high rates of morbidity and mortality due to increasing rates of drug-resistant infections, and inappropriate prescribing in primary care is common—fewer than half of outpatients and a fourth of inpatients receiving antibiotics are treated appropriately (Wang et al. 2014). Policies aiming to reduce antibiotic use and resistance have been implemented since 2004 with limited success; however, national-level commitment and motivation to address the issue remain high. In 2011 a three-year antibiotic resistance control program was launched, bolstered in 2012 by the introduction of administrative regulations for clinical use of antibiotics (Xiao and Li 2015).

The focus of the administrative regulations is building accountability for reducing resistance in hospitals by requiring the establishment of hospital committees and strategies, enforcing prescribing restrictions through audits and inspections, and allocating hospital funds based on the achievement of targets linked to reduced antibiotic use. Noncompliant hospitals risk being downgraded, and noncompliant staff face dismissal.

After the program began, prescribing of antimicrobials decreased by 10 to 12 percent for both hospitalized patients and outpatients from 2010 to 2012 (Xiao et al. 2013; Xiao and Li 2015). In 2012 the national essential drug list was updated, and in 2013 national guidelines for antimicrobial therapy were released, building on the momentum of antibiotic resistance control.

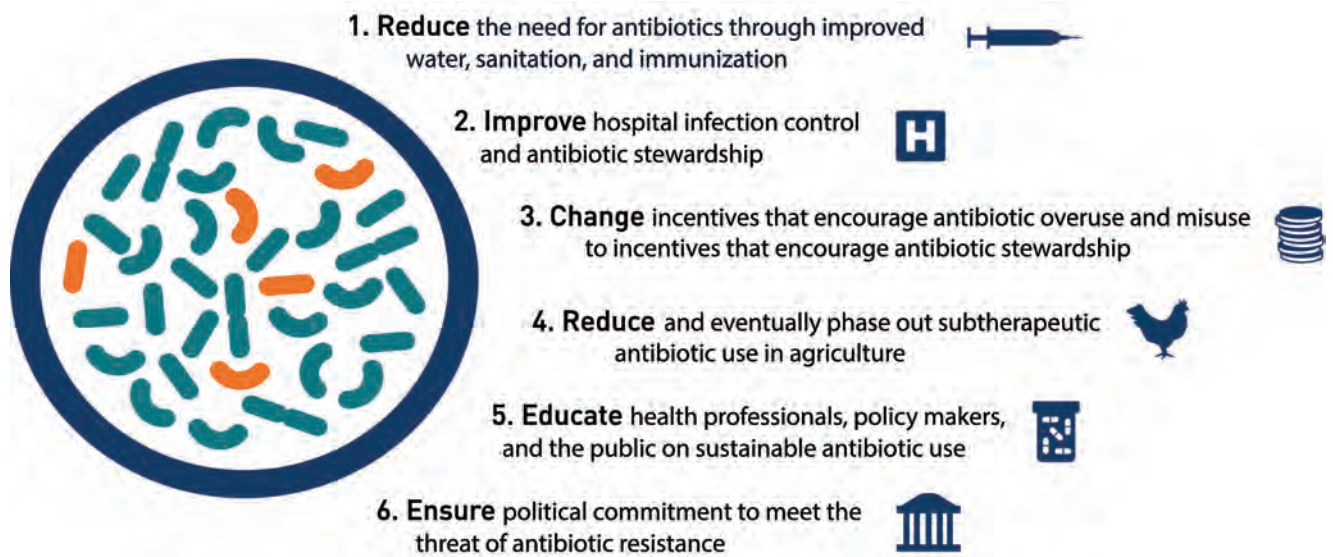


FIGURE 5-1: Six strategies needed in national antibiotic policies

treat common colds and acute diarrhea, regardless of whether the infection is viral or bacterial, vaccination against preventable, high-burden diseases like pneumonia and rotavirus can reduce antibiotic use (Box 5-2). The primary purpose of these public health measures is to improve people’s health and well-being; the “antibiotic-sparing” effect is an important side benefit. Implementation can take years because these measures involve multiple government departments and sectors—health, water, sanitation, agriculture, social development—and long-term

financial commitments. Antibiotic resistance strategies should support these goals but are unlikely to be the driving force behind their implementation.

2. Improve hospital infection control and antibiotic stewardship.

Infections can spread within hospitals, often through the hands of caregivers. Hand washing with soap or using alcohol disinfectant between patients and good environmental

BOX 5-2. THE ANTIBIOTIC-SPARING EFFECTS OF VACCINES

In the United States, the introduction of the pneumococcal vaccine in 2000 reduced pneumonia in children under two by nearly 40 percent (Grijalva et al., 2007). The vaccine also averted some 700,000 hospitalizations in adults 18 and older from 2000 to 2006 through herd immunity (Simonsen et al. 2011).

In addition to reducing the disease burden, the vaccine changed antibiotic use and resistance: antibiotic prescribing for acute otitis media in children under two fell by 42 percent (Zhou et al. 2008), and rates of resistant infections with serotypes included in the vaccine fell by 87 percent. Rates of infection with penicillin-resistant and multidrug-resistant strains of *Streptococcus pneumoniae* each dropped by more than 50 percent (Kyaw et al. 2006). In Canada, the introduction of free, population-wide influenza vaccines in Ontario in 2000 resulted in a relative decrease in antibiotic prescribing for respiratory infections of 64 percent (Kwong et al. 2009).

In South Africa, the introduction of the pneumococcal vaccine reduced pneumococcal infections with serotypes included in the vaccine by 83 percent in HIV-negative children and by 65 percent in HIV-positive children. Infection with penicillin-resistant strains fell by 67 percent, and infection with trimethoprim-sulfamethoxazole resistant strains dropped by 56 percent (Klugman et al. 2003).

Vaccines for viruses also avert antibiotic use—by preventing respiratory infections and acute diarrheas treated inappropriately with antibiotics (Hurwitz et al. 2000; Kwong et al. 2009; Polgreen et al. 2011). Influenza and pneumococcal vaccination reduce the risk of secondary bacterial infections from influenza (Simonsen et al. 2011; McCullers et al. 2014). Increasingly effective cholera vaccines (Qadri et al. 2015) demonstrate further potential for reducing the disease burden through vaccination.

Most studies of vaccine effects do not include direct estimates of antibiotic sparing, but it is clear that antibiotic use decreases with a lower burden of infectious disease.

cleaning are necessary but not sufficient to prevent the spread of infections. Other hospital-based interventions to improve antibiotic use include antibiotic stewardship programs and surveillance of resistance and hospital-acquired infections to guide clinical and policy decisionmaking.

INFECTION CONTROL

Healthcare-associated infections (HAIs)—infections contracted while a patient is being treated in a hospital or other healthcare facility—are primarily transmitted through the hands of healthcare workers (Pittet et al. 2006); by medical equipment, particularly intravenous and urinary catheters and ventilators (Cristina et al. 2013); and through contamination of the wound during surgery, often with bacteria from other areas of the patient's body (Anderson 2011). Some bacteria, such as *Clostridium difficile*, a diarrhea-causing pathogen spread through the fecal-oral route, are especially likely to spread through fingers, devices, and surfaces. The long-term use of antibiotics can destroy normal gut flora and increase susceptibility to *C. difficile* infection (Owens et al. 2008).

HAIs are responsible for 37,000 deaths and 16 million extra days of hospitalization in Europe, at a direct cost of €7 billion (WHO 2011a). The density of HAIs in intensive-care units in LMICs is twice as high as in Europe (Laxminarayan et al. 2013) and three times greater than in the United States (Allegranzi et al. 2011). Device-related infections are up to 19 times higher and surgical site infections are up to nine times higher in LMICs compared with high-income countries (WHO 2011a). Rates of HAIs in newborns in developing countries are up to 20 times the rates in developed countries (WHO 2011a).

Any new infection threatens patient health, but antibiotic-resistant bacterial HAIs are particularly dangerous and becoming more common (Klein et al. 2007). Drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriaceae (CRE) may be difficult and expensive to cure and can lead to longer hospitalizations than antibiotic-susceptible infections (Cosgrove et al. 2005). Fortunately, improving hand hygiene and introducing infection control programs with intervention “bundles” that target specific infections, such as catheter-associated urinary tract infections and ventilator-associated pneumonia, can prevent many HAIs. Infection control programs reduced nonprophylactic antibiotic use for heart surgery patients by more than 40 percent (DeRiso et al. 1996) and for urinary tract infection patients by more than 2 defined daily doses per day (Stéphan 2006). Improved infection control has also been shown to reduce the incidence of MRSA (Aldeyab 2008) and sepsis (Murthy and Nath et al. 2014).

HAND HYGIENE AND OTHER MEASURES

Hand washing or use of alcohol rubs by healthcare workers has been shown to reduce HAIs (Larson 1988, 1999; De Angelis et al. 2014), but the evidence base supporting the relationship could be stronger, including more randomized trials (Pittet et al. 2006; Allegranzi and Pittet 2009; Barnett et al. 2014). Current evidence does not allow a clear understanding of the importance of each component of hand hygiene interventions, which are often multimodal and

The density of healthcare-associated infections in intensive-care units in low- and middle-income countries is twice as high as in Europe and three times greater than in the United States.

may include behavioral, environmental, and stewardship components (McLaws 2015).

Despite the widespread acceptance that hand hygiene is important, fewer than half of healthcare workers in industrialized countries comply with hand hygiene guidelines (Erasmus et al. 2010). Barriers to hand hygiene include time constraints, understaffing, and (mainly in LMICs) lack of access to water and soap or antiseptics. Other reasons include irritation caused by frequent hand cleaning, perceptions that wearing gloves eliminates the need for it, lack of role models, and disagreement with or lack of knowledge of the recommendations (CDC 2002; WHO 2009).

Efforts to improve health workers' practices to reduce HAIs have focused on education and training (Kretzer and Larson 1998), with recent emphasis on structural, institutional, and motivational factors (Zingg et al. 2014; Pincock et al. 2012; Wilson et al. 2011).

ANTIBIOTIC STEWARDSHIP

Antibiotic stewardship programs (ASPs) can reduce inappropriate prescribing and provide other benefits, such as shorter therapies and lower hospital costs (Ohl and Dodds Ashley 2011). Both persuasive (advice or feedback on prescribing) and restrictive (limits or required approvals) interventions improve physicians' prescribing practices, and restrictive interventions have a larger effect. ASPs have also been associated with a decrease in HAIs (Davey et al. 2013).

Similarly, ASPs in critical-care units in nine countries from 1996 to 2010 reduced antibiotic use by 11 to 38 percent, lowered costs by \$5 to \$10 per patient per day, shortened the average duration of drug therapy, reduced rates of inappropriate use, and reduced the number of adverse events. After six months, ASPs were associated with reductions in antibiotic resistance for some drug-bug combinations, particularly for Gram-negative bacilli (Kaki et al. 2011). ASPs have also been found to reduce unnecessary antibiotic prescribing for asymptomatic bacteriuria (Trautner et al. 2015) and to decrease *C. difficile* incidence, particularly in geriatric settings (Feazel et al. 2014).

Although ASPs have been shown to reduce antibiotic resistance rates, few studies have demonstrated long-term reductions in resistance (McGowan 2012). However, given the lack of good measurement techniques and the long time required to observe the benefit of ASP programs, the lack of effect may be due to a lack of data rather than the absence of effectiveness.

Many hospitals in LMICs do not have ASPs (Box 5-3). ASPs are present in 14 percent of African hospitals, 46 percent of Latin American hospitals and 53 percent of Asian hospitals. This mirrors the proportion of countries in each region with

national antimicrobial stewardship standards: 20 percent in Africa versus 81 percent in Europe (Howard et al. 2014).

Compliance with ASP policies and guidelines can be enforced through regulations restricting antibiotic sales and prescribing at the hospital level. In Vietnam, Chile, and South Korea, interventions that include regulations decreased antibiotic use and resistance (Morgan et al. 2011). The same effect has been demonstrated to varying degrees in China (Xiao et al. 2013).

3. Change incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship.

Economic incentives can encourage the overuse of antibiotics all along the supply chain—in hospitals and communities and in agriculture. In many cases, the incentives may be a result of longstanding and accepted practices, such as physicians' selling drugs of all kinds directly to patients. Although some practices are common worldwide, most incentives are specific to the country and culture. An objective review of the major points of antibiotic sale can reveal who benefits and how actors' conscious or unconscious response to the incentives is likely to affect antibiotic use. Realigning incentives to promote antibiotic stewardship is challenging but achievable.

Where incentives for antibiotic overuse exist, they are most likely to affect hospitals, physicians, and other healthcare providers and pharmacists and other drug sellers. Doctors may benefit from prescribing a particular drug or more expensive drugs (Radyowijati and Haak 2003; Hulscher et al. 2010). Hospitals may also rely on antibiotics to treat infections that could be prevented with improved infection control.

Even in the United States, where antibiotic access, particularly to generic, first-line antibiotics, is nearly universal, a pharmacy program that offered customers free antibiotics with prescriptions influenced healthcare providers' behavior:

BOX 5-3. ANTIBIOTIC STEWARDSHIP TRAINING IN INDIA AND KENYA

Antibiotic stewardship training may be conducted at the hospital level or at workshops and trainings held in conjunction with broader meetings on antibiotic stewardship. Global Antibiotic Resistance Partnership (GARP) working groups have been involved in organizing a number of antibiotic stewardship trainings.

In India, GARP–India, the British Society for Antimicrobial Chemotherapy, and the Public Health Foundation of India sponsored a two-day training on antibiotic stewardship for healthcare workers following a policy forum on resistance and antibiotic stewardship in Indian hospitals. The British Society is also launching a massive open online course on antimicrobial stewardship in 2015 for Antimicrobial Chemotherapy and the University of Dundee.

In Kenya, antibiotic stewardship workshops have been held by GARP–Kenya following Infection Prevention Network conferences, and an antibiotic stewardship training course is planned for 2015.

Awareness campaigns have decreased antibiotic use, with some indications of corresponding decreases in resistance.

antibiotic prescribing increased by nearly 5 percent (Li and Laxminarayan 2015). Decreases in antibiotic prescribing after perverse financial incentives were eliminated have been demonstrated in China and Iceland (Song et al. 2014; Carbon and Bax 1998).

Incentives to improve antibiotic use have been components of hospital ASPs and include public recognition or financing for successful stewardship programs, and disincentives to overuse, such as enforcing hospital closures and staff dismissal for noncompliance with ASPs. However, changing incentives should not punish healthcare providers, for whom sales may be their only livelihood.

In Thailand, the Antibiotics Smart Use program, introduced in 2007, used behavior change interventions to reduce antibiotic prescribing while taking account of the financial effect of reduced prescribing under various hospital payment systems. A major finding of the program was that the provision of alternative therapies, such as herbal remedies, in place of antibiotics facilitated behavior change in physicians (Sumpradit et al. 2012). Effective solutions will need to be context specific, tailored to hospital and healthcare worker payment systems.

4. Reduce and eventually phase out subtherapeutic antibiotic use in agriculture.

In many parts of the world, food animals consume more antibiotics than humans do, and with even less oversight. The few available studies on antibiotic resistance in livestock show that farm animals carry a large load of resistant organisms. In most LMICs, little is known about antibiotic use in agriculture or antibiotic-resistant organisms in animals. Documenting levels and patterns of antibiotic use in agriculture will provide a sound basis for reviewing and strengthening laws and regulations. Incentivizing the rational use of antibiotics is important in the veterinary field as well (Tilman et al. 2002). Helping farmers optimize production as they transition to large-scale farming, for example, could avoid reliance on antibiotics in place of improved water, sanitation, and immunization (Laxminarayan et al. 2015).

5. Educate and inform health professionals, policymakers, and the public on sustainable antibiotic use.

Though international attention to the issue is growing, antibiotic resistance is still not widely recognized or understood as a serious threat to human health.

Awareness campaigns have decreased antibiotic use, with some indications of corresponding decreases in resistance (Huttner et al. 2010). In France, which had among the highest rates of antibiotic consumption in Europe, an awareness campaign with the slogan “Antibiotics are not automatic” resulted in an average 27 percent decrease in rates of antibiotic prescriptions between 2000 and 2007 across

all 22 regions of France. The decrease was greatest—36 percent—in children aged 6 to 15 years (Sabuncu et al. 2009).

The educational component of ASPs is often conducted at the hospital level, but guidance on antibiotic prescribing, antibiotic stewardship, and infection control can be incorporated into both undergraduate and postgraduate medical programs to instill appropriate prescriber practices early on. Medical students in Europe, the United States, and some LMICs reported interest in additional education on antibiotic prescribing (Dyar et al. 2014; Abbo et al. 2013; Thriemer et al. 2013).

A recent survey of 35 European medical schools found that all but one taught prudent antibiotic prescribing as a part of the undergraduate curriculum, but wide variation, both between and within countries, was detected in students' exposure to the principles. Only four of the 13 countries included had a national program for an antibiotic stewardship curriculum (Pulcini et al. 2014). In a selection of medical and pharmacy schools in five Southeast Asian countries in 2011, 87 percent of medical schools and 70 percent of pharmacy schools required education on antibiotic resistance (ReAct and Universiti Sains Malaysia 2011).

6. Ensure political commitment to address antibiotic resistance.

Generating local interest and pressure by healthcare professionals and the public and undertaking a thorough situation analysis are necessary to build political commitment and cooperation for combating antibiotic resistance. Thereafter, politicians need to allocate time, money, and resources to designing and implementing strategies to promote the rational use of antibiotics. In addition, government can convene academics and stakeholders from other government sectors—health, social development, environmental health, agriculture and food production, education, science and technology—to create locally relevant, evidence-based policies.

Examples of such political efforts include the Jaipur Declaration on Antimicrobial Resistance, in which WHO Southeast Asia member states committed to developing multisectoral national alliances to develop national antibiotic policies (WHO 2011c). WHO called for the creation of national-level strategies on antibiotic resistance in each member state as a part of its 2015 Global Action Plan (WHO 2015). The work of the Global Antibiotic Resistance Partnership is another example (Box 5-4).

South Africa released the Antimicrobial Resistance National Strategy Framework 2014–2024 in October of 2014. The framework, the culmination of several years of work, was set in motion by the publication of the GARP–South Africa situation analysis in the *South African Medical Journal* in 2011 (GARP–South Africa 2011). GARP and other partners generated national interest and spurred commitment to the issue over a very short time by leveraging data, champions, and existing regulatory efforts (Box 5-5).

BOX 5-4. FIVE LESSONS FROM THE GLOBAL ANTIBIOTIC RESISTANCE PARTNERSHIP

1. Creating an antibiotic resistance policy space

In most countries, at least some clinicians and experts on the ground are acutely aware of antibiotic resistance; however, policymakers have not yet recognized it as a priority. Therefore, a formal mechanism to connect the parties to spell out their concerns is an essential first step. A modest investment is enough to establish a working group with a mission of placing antibiotic resistance on the national agenda. Working group members can serve as volunteers, but a paid coordinator—ideally, a young professional or enthusiastic champion—is essential to maintain momentum and move the process forward.

2. Establishing a locus of national expertise

Working together, a group of scientific experts and stakeholders from all relevant disciplines (including agriculture, veterinary science, and human health) and sectors (government, nongovernmental organizations, private enterprise, and academia) can address the totality of issues related to antibiotic resistance in their countries, reach out to colleagues, and generate antibiotic knowledge. The working group becomes a trusted, unbiased source of advice to government and other sectors.

3. Documenting the antibiotic situation and context

Situation analyses and research build the platform on which future policies are based. In addition, they increase the legitimacy of the working group and its members. Conducting the analysis allows the working group to master the issue and inform and advise with authority. It also creates a sense of urgency and enthusiasm for action.

4. Engaging with government

Relationships with ministries of health and agriculture, in particular, are essential to the eventual development and implementation of antibiotic policies. These relationships may take the form of an external advisory group, a new group incorporated within a ministry, or a cooperative but informal advisory relationship.

5. Leading with action

Achieving national-level progress on antibiotic resistance takes time. Stakeholders need to become familiar with the issue, buy into the need to address the issue, and agree on how to do so. Several years are needed to generate evidence, awareness, and trust before national-level action can be implemented.

In the meantime, implementing interventions to improve antibiotic use legitimizes and raises the profile of working group members while achieving results through education, stewardship, awareness raising, and technical assistance.

BOX 5-5. KEYS TO PROGRESS IN KENYA AND SOUTH AFRICA

Kenya

Since it was established in 2008, the GARP–Kenya working group has involved the Ministry of Health in its activities. As a result, the Ministry assigned a national focal point for antibiotic resistance and established a multidisciplinary advisory committee in 2014. Three factors contributed to the success of the effort:

- maintaining consistent engagement with the government and other stakeholders about antibiotic resistance;
- using a variety of platforms to disseminate information and advocate for government action against antibiotic resistance; and
- providing authoritative documentation—the GARP–Kenya situation analysis—that served as a reference to influence government action and energize other stakeholders.

South Africa

The successful development of South Africa’s national strategy can be attributed to the following:

- passionate, enthusiastic national experts from various sectors;
- a champion in the National Department of Health who advocated for antimicrobial stewardship and infection prevention and control;
- reliable monthly data from credible sources, a warehouse for consolidation, and analysis and use of data in decisionmaking;
- functional, effective, efficient, and accessible laboratories and point-of-care diagnostics;
- regulatory support (the National Core Standards of Quality) to ensure facilities’ compliance with antibiotic stewardship principles; and
- funding for health facilities, particularly for public health centers and communities, and the inclusion of provincial and public doctors in discussions and plans.

CONCLUSIONS

Every country has a responsibility for maintaining antibiotic effectiveness. Successful efforts have direct benefits to local communities in the form of lower rates of antibiotic resistance, as well as to the global community and to future generations. New tools may make the job easier, but changing norms for antibiotic use and infection control (especially in hospitals) are effective means of reducing unnecessary and inappropriate use. Local expertise and

resolve are essential in every country. To date, it is mostly high-income countries that have established effective antibiotic use policies, but LMICs are also represented among the success stories. With global support, success should be achievable everywhere.

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