Chapter 18

Drug-Resistant Infections

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ANTIBIOTIC RESISTANCE

The global rise in antibiotic resistance threatens to undo decades of progress in treating infectious diseases caused by bacterial pathogens (Laxminarayan and others 2006). Resistance to the drugs used to treat malaria, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and *Mycobacterium tuberculosis* is also a serious concern, with multidrug-resistant and extensively drug-resistant tuberculosis now documented worldwide, particularly in China, India, and the Russian Federation (WHO 2014). These diseases and their treatments are covered in depth in other chapters in this volume. This chapter deals specifically with antibiotic resistance in the One Health framework of humans, animals, and the environment.

Bacterial resistance to first-line, second-line, and last-resort antibiotics is growing, although rates and trends vary by location, organism, and antibiotic (CDDEP 2016). Increased travel, trade, and migration mean that resistant bacteria can spread faster than ever (Du and others 2016; Johnson and Woodford 2013). The Centers for Disease Control and Prevention (CDC) considers *Clostridium difficile* (*C. difficile*), carbapenem-resistant Enterobacteriaceae, and cephalosporin-resistant *Neisseria gonorrhoeae* urgent threats to health in the United States (CDC 2013).

Drug-resistant infections are associated with higher morbidity, mortality, and health expenditures (Okeke, Laxminarayan, and others 2005). The burden of resistance falls heavily on low- and middle-income countries (LMICs), which typically have high burdens and rapid spread of infectious disease, poor nutrition, and increasing rates of antibiotic consumption in humans and animals, in addition to weaker health care systems and sparse standards and regulations that govern access, use, and quality of antibiotics (Okeke, Klugman, and others 2005).

Lack of access to antibiotics is still a serious concern for most LMICs. Pneumonia kills approximately 1 million children under age five each year, and an estimated 445,000 could be saved with the universal provision of antibiotics for community-acquired pneumococcal infections (Laxminarayan and others 2016). When they are available, first-line antibiotic treatments are still relatively affordable, but newer antibiotics needed to treat resistant infections may be out of reach in low-resource settings (Laxminarayan and others 2016; Mendelson and others 2015).

At the same time, resistant infections are becoming a significant cause of death, particularly for children. Mortality is higher for children with drug-resistant infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA, a common skin and soft tissue infection) and infections caused by extended spectrum beta-lactamase-producing bacteria (Kayange and others 2010). Though data are limited, it is estimated that resistant sepsis infections kill approximately 214,000 neonates each year, primarily in India, Pakistan, Nigeria, the Democratic Republic of Congo, and China (figure 18.1) (Laxminarayan and others 2016). The prevalence of drug-resistant infections in children is growing: the prevalence of

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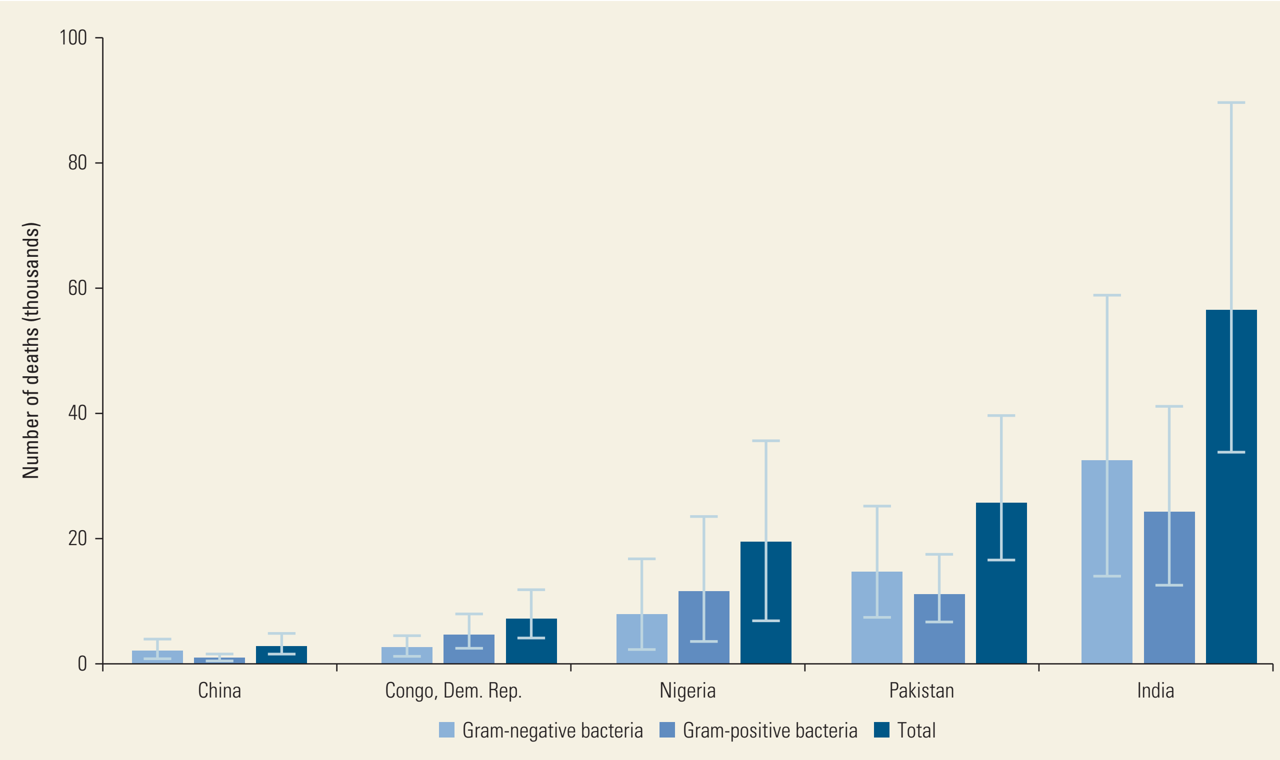
Figure 18.1 Estimated Neonatal Sepsis Deaths Caused by Bacteria Resistant to First-Line Antibiotics in High-Burden Countries



Source: Laxminarayan and others 2016.
Note: Bars represent maximum and minimum values from Latin Hypercube Sampling model.

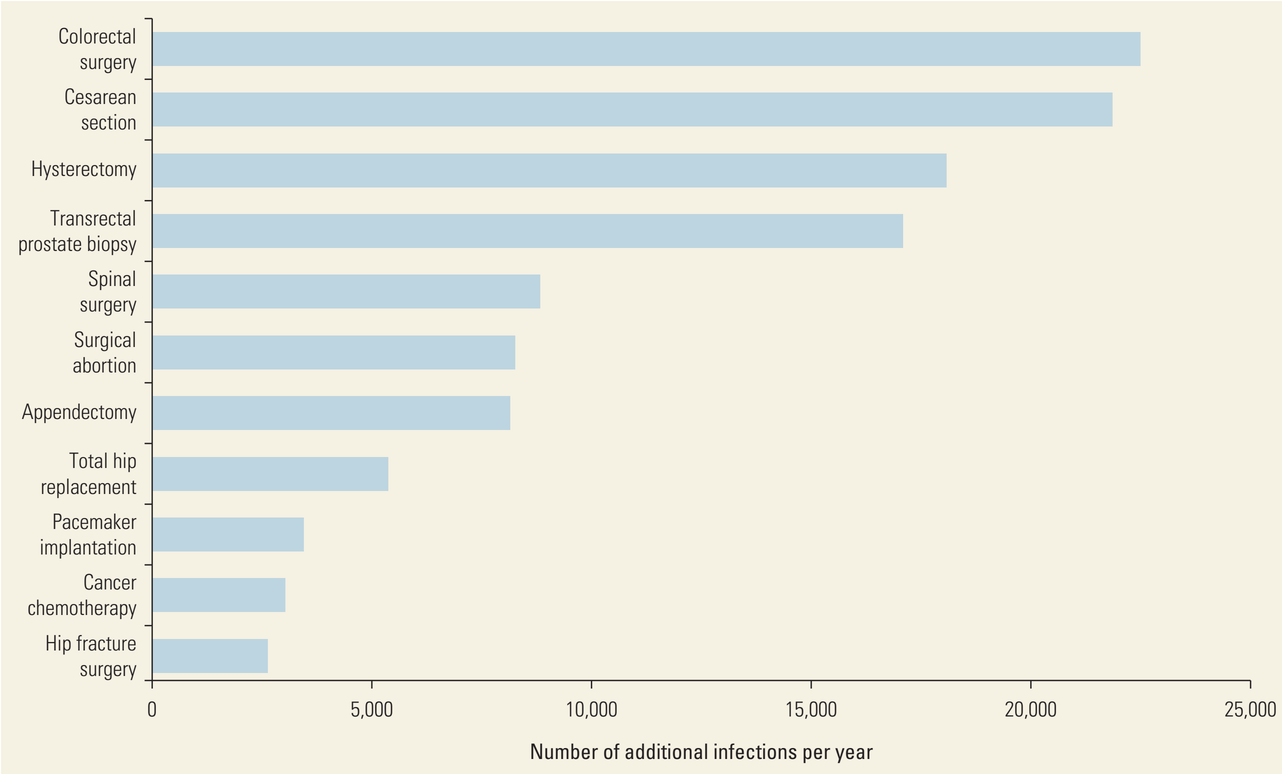
carbapenem-resistant *Enterobacteriaceae* infections in children increased from 0 percent in 2000 to 5 percent in 2012 in the United States (Logan and others 2015).

Drug-resistant typhoidal and nontyphoidal *Salmonella* infections are also on the rise, with multidrug resistance detected in 50 to 75 percent of nontyphoidal *Salmonella* isolates tested and up to 89 percent of *Salmonella* Typhi isolates tested in Sub-Saharan Africa (Al-Emran and others 2016; Kariuki and others 2015). The Typhoid Fever Surveillance in Africa Program also reported high levels of resistance in invasive *Salmonella* to first-line treatments, in addition to multidrug-resistant strains (Baker, Hombach, and Marks 2016). However, incidence of resistant *Salmonella* infections varies widely across the African region, indicating that national surveillance systems are needed to guide treatment decisions (Al-Emran and others 2016). Invasive *Salmonella* infections are responsible for approximately 600,000 deaths a year, particularly in children in low-resource settings. Case fatality rates from multidrug-resistant *Salmonella* Typhi infections in South Asia are 10 percent—approaching those of the pre-antibiotic era (Okeke, Laxminarayan and others 2005).

Many infections, both drug-resistant and drug-susceptible, are acquired in hospitals. Surgical site infections account for one-third of all health care–associated infections (HAIs) worldwide; they are the leading cause of HAIs in low-resource settings (Allegranzi and others 2011). Antibiotic prophylaxis can reduce the risk of infection in patients undergoing surgery and chemotherapy, but antibiotic resistance threatens to undo these benefits (Teillant and others 2015). A 30 percent decrease in antibiotic efficacy would lead to an estimated 120,000 additional infections and 6,300 additional deaths per year in the United States, according to a recent modeling study (figure 18.2). Other HAIs, particularly sepsis, are a danger for both neonates and their mothers, who are increasingly seeking birth and delivery care at hospitals at the advice of health care providers. Increasing rates of drug resistance in these infections amplify this risk.

Despite limited national-level data and a lack of standardized methods for collecting resistance data, it is clear that resistance is declining in some instances. Map 18.1 shows the global prevalence of MRSA. MRSA rates are decreasing in Canada, Europe, South Africa, and the United States (CDDEP 2016; EARS-Net 2014; Martin

Figure 18.2 Number of Additional Infections per Year Expected in the United States if Antibiotic Efficacy Decreased by 30 Percent



Source: Teillant and others 2015.

and others 2015). However, steep increases have been detected in several LMICs, including India (box 18.1), and what data are available in Africa indicate that rates are also high in some populations in the region (Abdulgader and others 2015). Even less information is available on MRSA and other bacterial infections in animals in LMICs.

Resistance of Enterobacteriaceae to one of the last-resort antibiotics, carbapenems, is low but increasing in many LMICs (CDDEP 2016; Lerner and others 2015). Extended spectrum beta-lactamases, which are resistant to most beta-lactam antibiotics, are also increasingly prevalent worldwide, including in Africa and Latin America (Datta and others 2012; Lu and others 2012; PAHO, forthcoming; Storberg 2014). Resistance to quinolones has been widely detected in enteric infections, such as those caused by *Escherichia coli (E. coli),* in Sub-Saharan Africa, where quinolone use has increased since generics became available in the early 2000s (Chattaway and others 2016). Sexually transmitted infections, such as *Neisseria gonorrhoeae*, are increasingly resistant to all available treatment options (Buono and others 2015).

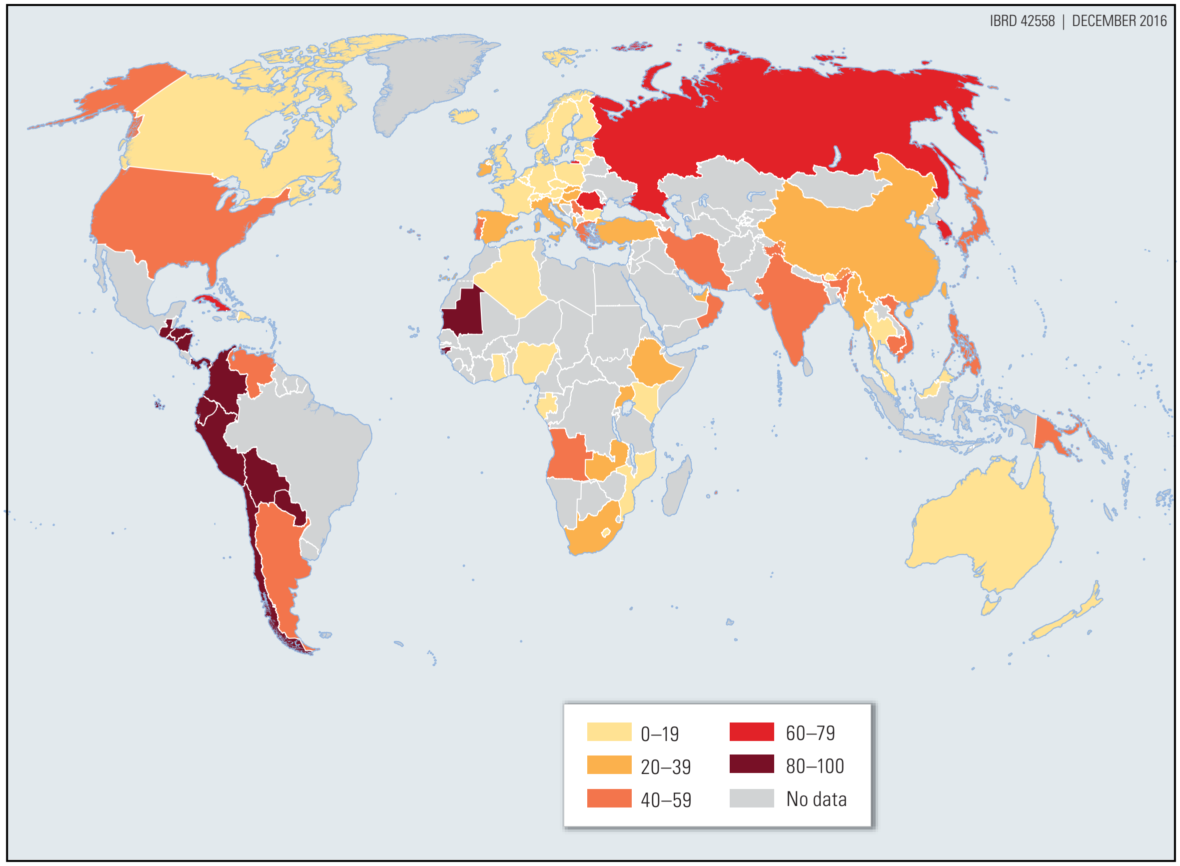
Resistant bacteria can also be detected in the guts of livestock or in water or soil that has been exposed to antibiotics. These drug-resistant bacteria can then spread to humans through direct contact with animals and infected food, water, or waste (Marshall and Levy 2011). Emerging resistance mechanisms, such as the MCR-1 gene conferring plasmid-mediated resistance to colistin, a last-resort antibiotic, have been detected in both humans and animals and have the potential to render even more infections untreatable (Liu and others 2016). Overall, there is a significant lack of surveillance data on resistance in humans and animals in most LMICs and in many high-income countries (HICs); these data are critical to guiding policy making and clinical care.

DRIVERS OF ANTIBIOTIC USE AND RESISTANCE

Use in Human Health Care

Every use of an antibiotic, whether appropriate or inappropriate, exerts selection pressure, giving resistant bacteria an advantage and accelerating the development of resistance. Consumption of antibiotics is rising globally, but particularly in LMICs, as a result, in part, of rising incomes and increased access to drugs.

Map 18.1 Percentage of Methicillin-Resistant *Staphylococcus aureus* Isolates, by Country, Most Recent Year, 2011–14



Sources: Abdulgader and others 2015; CDDEP 2016 (https://resistancemap.cddep.org); PAHO, forthcoming; WHO 2014.

Note: Where available, data from hospital-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and invasive isolates are 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, at least one of the following drugs was used to test for MRSA: cefoxitin, cloxacillin, dicloxacillin, flucloxacillin, methicillin, and oxacillin. Intermediate-resistant isolates are considered resistant in some calculations, as in the original data source. Data from Abdulgader and others (2015) collected before and during 2011 were included as 2011.

Box 18.1

Antibiotic Resistance in India

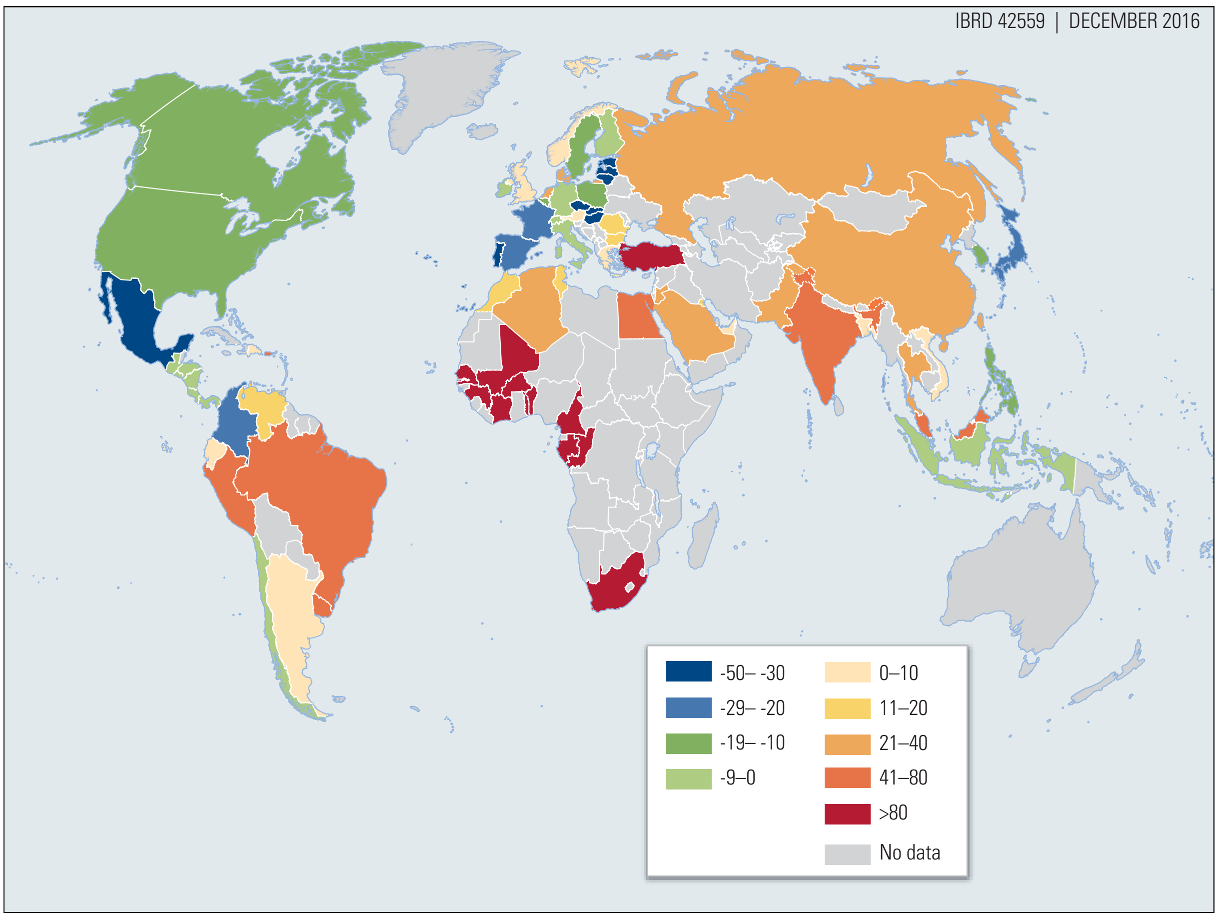
India has high levels of both antibiotic consumption and antibiotic resistance. Antibiotic use is increasing in conjunction with improved livelihoods and expanded access to drugs, providing benefits for human health. Still, over-the-counter sales without a medical provider's prescription, weak regulation, and poor incentives for rational use are contributing to inappropriate use of antibiotics. Owing in part to poor health infrastructure, poor-quality drugs, and a high burden of disease, India's rates of resistant infections are rising.

India was the top consumer of antibiotics in 2010 and one of the top global consumers of antibiotics in agriculture that same year. Consumption of faropenem, an oral antibiotic structurally similar to carbapenems, has increased by 154 percent since it was approved for use in 2010 (Gandra and others 2016). Strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* Typhi, and MRSA (methicillin-resistant *Staphylococcus aureus*) have high resistance to most antibiotics, including carbapenems. Improved regulation, behavior change for patients and providers, incentives for improved prescribing practices, and increased surveillance have the potential to reverse current trends while preserving and increasing gains in access (Laxminarayan and Chaudhury 2016).

Human antibiotic consumption is also driven by the burden of infectious disease, as well as by economic, behavioral, environmental, and structural factors. Expanded insurance coverage and increased physician density increase the consumption of antibiotics (Klein and others 2015; Zhang, Lee, and Donohue 2010). Decision fatigue and patient demand also increase antibiotic prescribing (Dosh and others 2000; Linder and others 2014). Antibiotic use is also correlated with season, increasing in the winter (December through February in the northern hemisphere and August through September in the southern hemisphere) when the incidence of infectious disease is higher (Sun, Klein, and Laxminarayan 2012). In addition to driving resistance, antibiotic use increases the incidence of *C. difficile* infection, which takes hold when antibiotic treatment has destroyed the normal gut flora. *C. difficile* is responsible for an estimated 14,000 deaths per year in the United States (CDC 2013).

As shown in map 18.2, it is estimated that antibiotic consumption increased more than 30 percent in 71 countries between 2000 and 2010, reaching approximately 70 billion standard units (single-dose units) in 2010 (Van Boeckel and others 2014). This increase was primarily in first-line classes of antibiotics, including penicillins and cephalosporins, which together make up more than half of global consumption. Use of last-resort antibiotic classes such as carbapenems and polymixins also increased. Although the consumption of antibiotics

Map 18.2 Percentage Change in Antibiotic Consumption per Capita, by Country, 2000–10



Source: Van Boeckel and others 2014, based on IMS MIDAS.
Note: 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, the Republic of Congo, Côte d'Ivoire, Gabon, Guinea, Mali, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings to which they belong. For countries with no data 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), the Netherlands (2005), and Vietnam (2005). Much of the increase in antibiotic consumption in South Africa can be attributed to the use of co-trimoxazole as prophylaxis for HIV (human immunodeficiency virus) patients as recommended by the World Health Organization.

declined in some HICs from 2000 to 2010, annual per capita consumption in the United States is still one of the highest in the world, at approximately 22 standard units per person (map 18.2). Consumption grew fastest in middle-income countries, including Brazil, China, India, Russia, and South Africa.

Human consumption of antibiotics is often inappropriate in both LMICs and HICs, where antibiotics are purchased over the counter or prescribed incorrectly by a physician when they are not needed and will not be effective. Diarrheal and respiratory infections are frequently treated with antibiotics in the absence of diagnostics, even if such practice brings no benefit to patients; both consumers and prescribers may lack the awareness, education, or incentive to use antibiotics correctly.

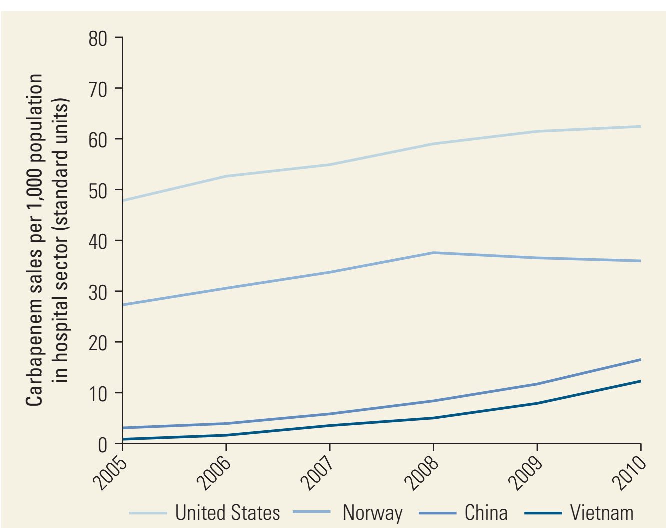
An estimated 80 percent of antibiotics globally are purchased outside of hospitals (Kotwani and Holloway 2011). Although many of these antibiotics are purchased without prescriptions, increased regulation to restrict sales may not be an appropriate solution for communities that lack access to antibiotics. Interventions that target incentives linked to consumers, prescribers, and retailers and that educate the public and health care providers will be required to change consumption patterns in communities.

Use in Hospitals

The volume of antibiotic consumption is greater in communities, but the clinical consequences of resistance are greater in hospitals, which are home to a rotating population of seriously ill patients treated heavily with medications, including antibiotics. Infections treated in hospitals may originate at the point of care (HAIs) or in communities, where patients may have already been treated unsuccessfully with antibiotics.

Suboptimal prescribing of antibiotics is common in both LMICs and HICs. In Nepal, an estimated 10 percent to 40 percent of antibiotic use is inappropriate; in Vietnam, one-third of hospital prescriptions were deemed inappropriate (Paudel, Sharma, and Das 2008; Shankar and others 2007; Thu and others 2012). In six hospitals in the United States, initial antibiotic therapy was changed after five days in only one-third of patients, although 58 percent of patients tested negative for bacterial infection (Braykov and others 2014). The use of carbapenems is rapidly increasing in hospitals (figure 18.3) (CDDEP 2016). In some countries (for example, China), doctors or hospitals profit from the volume of antibiotics sold (Currie, Lin, and Meng 2014).

Figure 18.3 Per Capita Carbapenem Use in the Hospital Sector, 2005–10



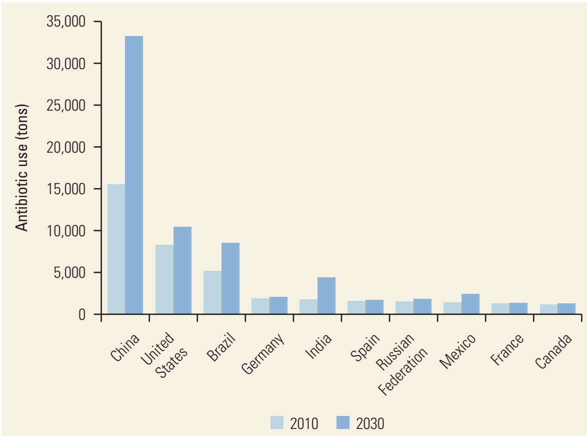
Source: Based on IMS MIDAS.

Use in Food Animal Production

At least two-thirds of all antibiotics, including those important for human medicine, are estimated to be used in livestock production at subtherapeutic levels to promote growth and prevent disease, and at therapeutic levels to treat disease (Laxminarayan, Van Boeckel, and Teillant 2015). Antibiotic use in animal agriculture is widespread and is estimated to increase by more than two-thirds between 2010 and 2030 (Van Boeckel and others 2015). This widespread use creates strong selection pressure, encouraging the emergence and development of resistance (Laxminarayan, Van Boeckel, and Teillant 2015).

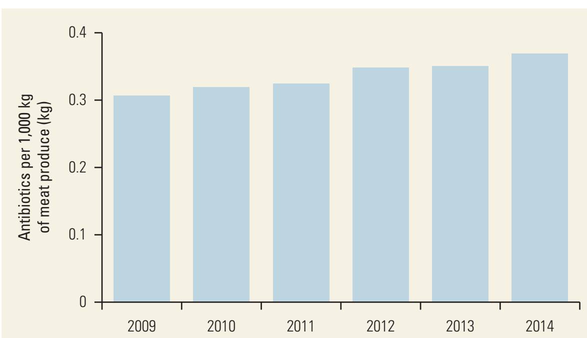
In animal production systems, antibiotics have long been used in place of improved sanitation and hygiene to prevent disease. As incomes rise in LMICs, the demand for animal-source food products will grow (Gelband and others 2015). To meet this demand, more farmers are using intensive production systems, with more animals raised in smaller spaces, leading to greater reliance on antibiotics to prevent disease and promote growth. In the coming decades, antibiotic use for food production is predicted to grow, as shown in figure 18.4, with Brazil, China, India, Russia, and South Africa expected to experience an estimated 98 percent increase collectively (Laxminarayan, Van Boeckel, and Teillant 2015). Consumption is also increasing in some HICs. Figure 18.5 illustrates increasing antibiotic use in meat production in the United States, where antibiotic use per unit of meat has increased every year from 2009 to 2014 (CDDEP 2016).

Figure 18.4 Estimated Growth in the Consumption of Antibiotics in Livestock, Top 10 Countries, 2010-30



Source: Van Boeckel and others 2015.

Figure 18.5 Antibiotic Use in Meat Production in the United States, 2009–14



Sources: USDA 2015; U.S. Department of Health and Human Services 2015.
Note: kg = kilograms.

NATIONAL POLICIES TO CONSERVE ANTIBIOTIC EFFECTIVENESS

The World Health Assembly passed the Global Action Plan on Antimicrobial Resistance in May 2015 (WHO 2015). The plan calls on member countries to establish national plans to address antibiotic consumption and resistance within the next two years. Plans are expected to be context specific and ideally will encompass five strategic objectives:

- Improving awareness through education or awareness campaigns
- Strengthening existing evidence through surveillance and monitoring
- Reducing the risk of infections through prevention measures
- Optimizing the use of antibiotics through stewardship and appropriate prescriptions
- Reshaping economic incentives to encourage research on new antibiotics while preserving existing drugs.

Some HICs, such as the United Kingdom and the United States, have implemented comprehensive national action plans. Fewer LMICs have such plans, but in those LMICs that do, the plans have proved successful. Progress in Ethiopia, Nepal, South Africa, and Vietnam shows that action plans are both possible to formulate in LMIC settings and are urgently needed; box 18.2 describes South Africa's plan.

COST-EFFECTIVE INTERVENTIONS

Although data on antibiotic use and resistance in LMICs are limited, new surveillance networks and laboratory-strengthening programs are being established. Online databases like the Center for Disease Dynamics, Economics & Policy's ResistanceMap[1] are filling the gap by providing data on use and resistance for a significant number of countries. Evidence on effective interventions is limited by the diversity of resistance drivers and the long timelines required to observe an effect on antibiotic resistance rates. A review found that the evidence base for specific national interventions is insufficient to inform policies (Dar and others 2015), but areas for action have clear potential benefits (Holloway 2011; Jamison and others 2013).

Water, Sanitation, and Hygiene

In the United States, the burden of infectious diseases declined before the introduction of antibiotics, largely because of improvements in water and sanitation. Many LMICs use antibiotics as a substitute for these improvements, but medications alone will not achieve the same reductions. Handwashing, clean water, and excreta disposal reduce diarrheal diseases by 48 percent, 17 percent, and 36 percent, respectively (Cairncross and others 2010). Handwashing also reduces respiratory infections by at least 16 percent (Rabie and Curtis 2006). Handwashing by health care providers reduces HAIs and the development and spread of resistant infections (Allegranzi and Pittet 2009; De Angelis and others 2014).

Sanitation and water quality require expensive infrastructure, but the savings from averted diseases offset most investments in water, sanitation, and hygiene (Clasen and Haller 2008). Water supply and sanitation interventions are cost-effective in all regions (Hutton, Haller, and Bartram 2007). Hand hygiene is highly

Box 18.2

Comprehensive National Action Plans: The Example of South Africa

The South African Department of Health launched a national strategic framework in 2014 (Department of Health, South Africa 2014) that adopted recommendations set by the World Health Organization and the International Committee of the World Organisation for Animal Health to curb the threat of antibiotic resistance. Key elements of the framework include strengthening, coordinating, and institutionalizing interdisciplinary efforts through national and governance structures; optimizing surveillance and early detection of antibiotic resistance; enhancing infection prevention and control; and promoting appropriate use of antibiotics in animal and human health. Several interventions have been proposed to ensure success, including amendments to medical curricula; improved hand hygiene, vaccination, and water and sanitation; establishment of hospital antibiotic stewardship programs; and review of antibiotics approved for use in animal feed.

Early detection and strong surveillance are essential for capturing trends and creating evidence-based public policies. South Africa's national strategy framework aims to strengthen the existing surveillance system by developing an early warning system for potential disease outbreaks and by tracking trends and resistance patterns. In the long term, it will also use local, regional, and national resistance patterns to optimize prescribing and report on resistance rates in food-producing and companion animals.

cost-effective and the most affordable intervention at US$3.35 per disability-adjusted life year (DALY) averted (Cairncross and Valdmanis 2006).

Vaccination

The potential reduction in antibiotic use attributable to vaccination is considerable. An estimated 11 million days of antibiotic treatment could be avoided by the universal introduction of the pneumococcal vaccine (Laxminarayan and others 2016). Influenza in the United States is nearly perfectly predicted by antibiotic sales data (Polgreen, Laxminarayan, and Cavanaugh 2011). An estimated 20 percent reduction in influenza would reduce antibiotic prescribing by 8 percent in the United States; a universal vaccination program in Ontario, Canada, was found to reduce influenza-associated antibiotic prescribing by 64 percent (Kwong and others 2009; Polgreen, Laxminarayan, and Cavanaugh 2011). Influenza vaccination also averts secondary bacterial infections, which have been associated with up to 40 percent of influenza cases that require hospitalization (Falsey and others 2013; McCullers 2014). The introduction of vaccines for viral and bacterial diarrheal infections, such as rotavirus and cholera, are likely to achieve similar reductions in antibiotic use (Ganguly and others 2011; Okeke 2009).

Vaccination can reduce the overall disease burden and the incidence of drug-resistant infections. The introduction of the pneumococcal vaccine in the United States reduced infection with both penicillin-resistant and multidrug-resistant strains of *Streptococcus pneumoniae*—incidence of each type dropped more than 50 percent (Grijalva and others 2007; Kyaw and others 2006). Similarly, in South Africa, introduction of the vaccine reduced infection with penicillin-resistant strains by 67 percent and infection with trimethoprim-sulfamethoxazole-resistant strains by 56 percent (Klugman and others 2003). Vaccines also reduce antibiotic resistance by reducing overall selection pressure (Gelband and others 2015; Kwong and others 2009; Polgreen, Laxminarayan, and Cavanaugh 2011). Vaccines are being developed for commonly resistant infections, such as those caused by *Staphylococcus aureus*, *E. coli*, and *Klebsiella pneumoniae*, as well as *C. difficile*, but have faced significant challenges (Gelband and others 2015).

The cost-effectiveness of introducing new vaccines will differ by background burden of disease and existing cold chains; most vaccines are highly cost-effective, even though assessments rarely include the savings from reducing drug-resistant infections (Maurice and Davey 2009; Rheingans and others 2014). In India, health care cost savings offset the cost of vaccination against *Haemophilus influenzae* in all states (Clark and others 2013). Similarly, an assessment of cost-effectiveness in LMICs found that the *Haemophilus influenzae* type b conjugate vaccine was cost saving or highly cost-effective

(Griffiths, Clark, and Hajjeh 2013), while the pneumococcal vaccine was highly cost-effective in 68 of 72 developing countries (Sinha and others 2007). For diarrheal infections, the rotavirus vaccine provided economic benefits at diverse prices, while cholera vaccination had economic benefits in specific contexts (Rheingans and others 2014).

Antibiotic Stewardship and Infection Control Programs in Hospitals

Stewardship and infection control have been broadly proposed as the most effective interventions for reducing antibiotic use in all settings (Dar and others 2015). Components of stewardship programs such as prescription audits, peer comparisons, and guidelines have successfully reduced antibiotic use (Meeker and others 2014; Meeker and others 2016). Hospital antibiotic stewardship programs aim to provide the correct dose of the most appropriate antibiotic at the right time; they have also been shown to reduce antibiotic use by 11 percent to 38 percent and to be associated with modest reductions in antibiotic-resistant infections (Kaki and others 2011).

Antibiotics are often used as a substitute for infection prevention and control in hospitals. Infection control programs reduce antibiotic use, in addition to reducing the prevalence and spread of HAIs. They are particularly important in LMICs, where rates of HAIs are two to three times higher than in Europe and the United States (Allegranzi and others 2011; Davey and others 2005; WHO 2011). Bundled interventions and handwashing have been shown to reduce both HAIs and antibiotic use (Gelband and others 2015).

Multifaceted infection control programs have been shown to be cost-effective in the United States (Dick and others 2015). Although evidence from LMICs is limited, the higher burden of HAIs in LMICs indicates that these interventions would be highly effective there as well. The cost-effectiveness of antibiotic stewardship programs may depend on the prevalence of antibiotic resistance. Extensive evidence indicates that stewardship programs reduce the length of hospital stays and expenditures on antibiotics (CDC 2016), and that antibiotic stewardship teams can be cost-effective in improving care for bacteremia in the United States (Scheetz and others 2009).

Incentives for Rational Use

Delinking the prescribing of antibiotics from financial incentives or creating financial incentives for improved prescribing can reduce the use of antibiotics (Carbon and Bax 1998; Song and others 2014). For example, a Chinese program linked hospital payments to targets for reduced antibiotic use, alongside the introduction of prescribing regulations, audits, and inspections. Following the program, prescribing declined between 10 percent and 12 percent (Xiao and others 2013).

There are no studies that directly assess the cost-effectiveness of incentives or regulations to reduce antibiotic use. However, lessons can be drawn from several historical examples: persons with free medical care in the United States used 85 percent more antibiotics than did persons who paid for a portion of care, while cost sharing reduced both inappropriate and appropriate antibiotic use (Foxman and others 1987). A free antibiotics program introduced in the United States in 2006 increased antibiotic prescribing, with prescribers shifting to drugs covered under the program (Li and Laxminarayan 2015). A prescription audit study in China found that financial incentives determined prescribing patterns: physicians were more likely to prescribe antibiotics when patients indicated they would purchase the antibiotics at hospitals (Currie, Lin, and Meng 2014).

Reduction of Antibiotic Use in Agriculture

National regulation is one way to encourage reductions in antibiotic use in food animal production. The use of antibiotics to promote growth has been banned in the European Union since 2006. Although some farmers simply shifted to using antibiotics for prevention rather than for growth, the bans resulted in decreasing or consistently low use of antibiotics in agriculture in many European Union countries, including Sweden and Denmark (Cogliani, Goossens, and Greko 2011). Few LMICs have introduced such bans.

Many countries have been reluctant to ban agricultural use of antibiotics because of potential adverse economic impacts on their livestock sectors, but research shows that the impact is minimal in farming systems that are already optimized with respect to the genetic potential of herds, hygiene, nutrition, and herd health (Laxminarayan, Van Boeckel, and Teillant 2015). Some countries have banned or discouraged the use of certain antibiotic growth promoters (table 18.1). The U.S. Food and Drug Administration issued guidelines in 2013 asking the pharmaceutical industry to restrict the use of antibiotics as growth promoters (Laxminarayan, Van Boeckel, and Teillant 2015). Vaccination can also prevent disease and antibiotic use in animals, as it does in humans.

Evidence from HICs suggests that the economic impact of removing growth promoters is low, but the impact may be different in LMICs where antibiotics are

Table 18.1 Regulation of Antibiotic Use in Livestock in OECD Countries

Country	Ban on antibiotic growth promoters	Prescription required
Australia	No, but some AGPs banned (fluoroquinolones, avoparcin, and others)	Yes, prescription required for most veterinary antibiotics
Canada	No, voluntary phaseout notice issued in April 2014 that mimics the U.S. FDA approach	No, plan to strengthen veterinary oversight developed in line with the U.S. FDA approach
Chile	No data	No data
European Union member states	Yes, all AGPs banned in 2006	Yes
Israel	No data	No data
Japan	No	Yes
Mexico	Yes, AGPs banned in 2007 with exceptions (avoparcin, vancomycin, bacitracin, tylosin, virginiamycin, and others)	Yes
New Zealand	Yes, for critically and highly important antibiotics as listed by the WHO and the OIE	Yes, for antibiotics identified as having potential for resistance problems
Korea, Rep.	Yes, AGP use discontinued in 2011 until a veterinary oversight system can be put in place	Yes, veterinary oversight system in development
Turkey	No data	No data
United States	No, voluntary guidelines to withdraw the use of medically important antibiotics as promoters released by U.S. FDA in 2013	No, under new U.S. FDA guidance, use of medically important antibiotics to be under the oversight of licensed growth veterinarians

Sources: Table adapted from Laxminarayan, Van Boeckel, and Teillant 2015. Australian Commission on Safety and Quality in Health Care 2013; European Union 2003; Government of Canada 2014; MAF New Zealand 2011; Maron, Smith, and Nachman 2013; USDA 2011, 2013; U.S. FDA 2013.
Note: AGP = antibiotic growth promoter; OECD = Organisation for Economic Co-operation and Development; OIE = World Organisation for Animal Health; U.S. FDA = U.S. Food and Drug Administration; WHO = World Health Organization.

still used in place of hygiene and other measures to optimize production. In China, the economic costs of a ban could reach billions of dollars but would still be significantly less than the economic burden of resistant infections (Laxminarayan, Van Boeckel, and Teillant 2015).

Education and Awareness

Campaigns have successfully reduced human antibiotic use in HICs, but evidence from LMICs is sparse (Huttner and others 2010). Awareness campaigns in France and Belgium reduced antibiotic prescribing by 27 percent and 36 percent, respectively, and both programs saw some reduction in resistant pneumococci (Sabuncu and others 2009). Some LMICs have begun to initiate awareness campaigns coinciding with the CDC's Get Smart About Antibiotics Week and the World Health Organization's (WHO) World Antibiotic Awareness Week (Global Antibiotic Resistance Partnership 2015). Few national-level campaigns have specifically targeted use in animals. As with antibiotic stewardship programs, awareness campaigns that reduce use also reduce expenditures on antibiotics, and the campaigns in Belgium and France were associated with significant savings (Huttner and others 2010). However, the cost-effectiveness of such campaigns has not been formally assessed, especially in LMICs.

Education without incentives or oversight may be less successful at changing behavior. Interventions targeted toward prescribers and consumers that combined education with managerial oversight have been more successful at reducing inappropriate antibiotic use than have educational materials alone (Holloway 2011). In Asia, health care provider interventions to increase appropriate use have typically been more successful than have other interventions to reduce use, unless they have been accompanied by oversight mechanisms such as peer review (Holloway 2011).

Surveillance of Antibiotic Use and Resistance

Surveillance of antibiotic use and resistance in humans and animals is needed to inform clinical decision making and national policies. Although few LMICs have comprehensive national surveillance programs, private sector laboratories often collect detailed data on resistance and are an underused resource in many data-scarce areas. These laboratories provide valuable additions to public sector resistance data in countries such as India and South Africa, where more than 98 percent and 80 percent, respectively, of accredited medical laboratories are in the private sector (CDDEP 2016; Gandra, Merchant, and Laxminarayan 2016).

Regional surveillance networks collect data in Latin America (Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos [ReLAVRA]), Asia (Asian Network for Surveillance of Resistant Pathogens [ANSORP]), Central Asia and Eastern Europe (Central Asian and Eastern European Surveillance of Antimicrobial Resistance [CAESAR]), and Europe (European Antimicrobial Resistance Surveillance Network [EARS-Net]). ResistanceMap, a global repository of antibiotic resistance and use data, incorporates these and other data from surveillance networks and private laboratories in LMICs into a visualization interface that can be used to assess national patterns and trends.

New Drugs and Antibiotic Alternatives

The pipeline of new antibiotics is relatively robust, with 7 new antibiotics approved in 2014 and 37 under development (Pew Charitable Trusts 2014); however, new drugs will always be needed as resistance develops, particularly for serious threats such as Gram-negative bacteria and for use in low-resource settings. The financial incentives to develop antibiotics are limited compared with other drugs because of their short course of use and potentially restricted use, among other barriers. Several initiatives—including the United Kingdom's *Review on Antimicrobial Resistance*; the Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) partnership funded by the Innovative Medicines Initiative; and the Global Antibiotic Research and Development Partnership, established under the auspices of the Drugs for Neglected Diseases *initiative* (DND*i*) and the WHO—are seeking to address these barriers to ensure a robust antibiotic pipeline (O'Neill 2016).

Because resistance to all antibiotics naturally develops, alternatives to antibiotics present other options. Alternatives include vaccines and improved diagnostics, as well as antibodies, probiotics, lysins, bacteriophages, immune simulation, and peptides. Development of a complete portfolio of these alternatives will take an estimated 10 years and cost a minimum of US$2.1 billion (Czaplewski and others 2016).

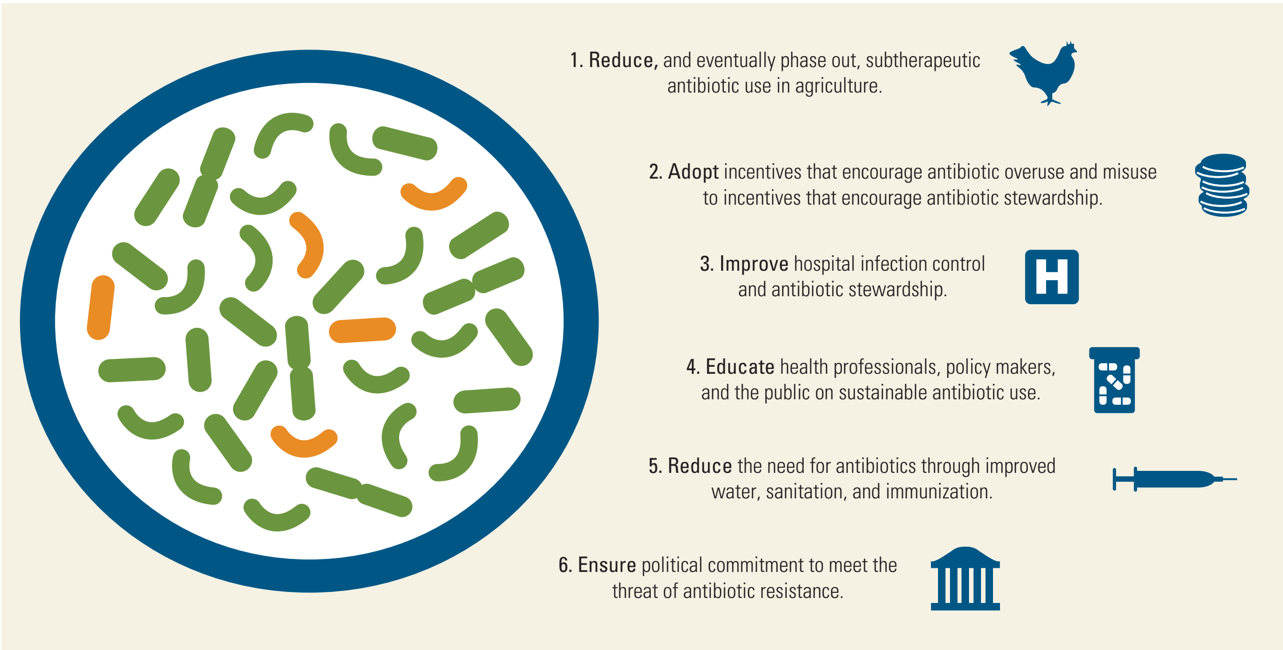
CONCLUSIONS

National action, tailored to local contexts and patterns of resistance, is key to curbing the global threat of antibiotic resistance. The Global Antibiotic Resistance Partnership, which develops local capacity in LMICs to design and implement national antibiotic resistance plans, has identified six key interventions to curb antibiotic resistance (figure 18.6).

The following recommendations should be part of any national plan:

- *Reduce and eventually phase out subtherapeutic antibiotic use in agriculture.* Improved sanitation and hygiene at the farm level would reduce the need for prophylactic antibiotics. Antibiotic use in animal agriculture should be reduced, focusing on involving farmers and the agricultural industry in carefully phasing out the use of growth promoters and premixed animal feeds (Laxminarayan, Van Boeckel, and Teillant 2015).
- *Adopt incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship.* Making sure that payments are not linked to prescribing, as well as introducing rewards for compliance, may improve prescribing patterns.
- *Improve hospital infection control and antibiotic stewardship.* Antibiotic stewardship programs, infection prevention and control, and especially handwashing with soap can reduce infections, antibiotic use, and resistance while improving patient outcomes.
- *Educate health professionals, policy makers, and the public on sustainable antibiotic use.* Although public awareness is growing that antibiotic resistance presents a threat, there is little awareness of the individual actions that can be taken to reduce use. Patients, parents, health care providers, stakeholders, and hospital leaders all need to be aware of what they can do to reduce unnecessary use.
- *Reduce the need for antibiotics through improved water, sanitation, and immunization.* Disease prevention achieves the dual purposes of keeping people healthy and saving antibiotic doses. Water, sanitation, hygiene, and vaccination should be core components of any public health system.
- *Ensure political commitment to meet the threat of antibiotic resistance.* Without national commitment in the form of implemented action plans, the long-term sustainability of efforts to curb antibiotic resistance will be weakened. Although international efforts to curb antibiotic resistance have focused largely on national action, international support is also needed, particularly to stimulate private and public sector research to fill knowledge gaps and develop new drugs, diagnostics, and other technologies, as well as to strengthen laboratories for improved surveillance.

Figure 18.6 Six Strategies Needed in National Antibiotic Policies



Source: Gelband and others 2015.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  - (a) lower-middle-income = US$1,046 to US$4,125
  - (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

Data from figure 18.3 and map 18.2 are from 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.

1. https://resistancemap.cddep.org.

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