Chapter __. Drug-Resistant Infections

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Antibiotic Resistance
Drivers of Antibiotic Use and Resistance
   Use in Human Health Care
   Use in Hospitals
   Use in Food Animal Production
National Policies to Conserve Antibiotic Effectiveness
Cost-Effective Interventions
   Water, Sanitation, and Hygiene
   Vaccines
   Antibiotic Stewardship and Infection Control Programs in Hospitals
   Incentives for Rational Use
   Reducing the Use of Antibiotics in Agriculture
   Education and Awareness
   Surveillance of Antibiotic Use and Resistance
   New Drugs and Antibiotic Alternatives
Recommendations

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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 (HIV)/acquired immunodeficiency syndrome (AIDS), and 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 treatment are covered in depth in other chapters in this volume. This chapter deals specifically with antibiotic resistance in humans and animals.

Bacterial resistance is growing to first-line, second-line, and last-resort antibiotics, although rates and trends vary by location, organism, and antibiotic (CDDEP n.d.). Increased travel, trade, and migration mean that resistant bacteria can spread faster than ever before (Du and others 2016; Johnson and Woodford 2013).

Drug-resistant infections are associated with higher morbidity and mortality and higher 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 high rates of antibiotic consumption, in addition to weaker health care systems and sparse standards and regulations governing access, use, and quality (Okeke, Klugman, and others 2005).

Lack of access to antibiotics is still a serious concern for most LMICs. First-line antibiotic treatments are still relatively affordable, but newer antibiotics needed to treat resistant infections may be out of reach (Laxminarayan and others 2015; Mendelson and others 2015).
Pneumonia kills nearly 1 million children under five each year, and an estimated 440,000 could be saved with the universal provision of antibiotics for community-acquired pneumococcal infections (Laxminarayan 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) and extended spectrum beta-lactamase (ESBL) producing bacteria (Kayange and others 2010). Resistant sepsis infections kill an estimated 214,000 children each year, primarily in China, the Democratic Republic of Congo, India, Nigeria, and Pakistan (figure ___ .1) (Laxminarayan and others 2015). The prevalence of drug-resistant infections in children is growing: carbapenem-resistant Enterobacteriaceae (CRE) in children increased from 2000 to 2012 in the United States (Logan and others 2015).

<<figure ___ .1 about here>>

Figure ___ .1: Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in high-burden countries

*Source:* Laxminarayan and others 2016
Drug-resistant typhoidal and non-typhoidal *Salmonella* infections are also on the rise, with multidrug resistance of up to 70 percent detected in non-typhoidal *Salmonella* in sub-Saharan Africa and up to 30 percent in typhoidal *Salmonella* in Asia and Africa (Kariuki and others 2015). Invasive *Salmonella* infections are responsible for 600,000 deaths a year, particularly in children in low-resource settings. Case fatality rates from multi-drug resistant *S. typhi* infections in south Asia are 10 percent - approaching those of the pre antibiotic era (Okeke and others 2005).

Many drug-resistant infections are acquired in hospitals. Surgical site infections account for a third of all healthcare associated infections (HAIs) worldwide, and are the leading cause of infection 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 is estimated to be associated with 120,000 additional infections and 6,300 additional deaths per year in the United States alone (figure __.2). Healthcare associated infections, particularly sepsis, are not only a danger for neonates, but for their mothers, who are increasingly coming to hospitals to give birth at the advice of healthcare providers.

<<figure __.2 about here>>

Figure __.2: Number of additional infections per year in the United States under a 30 percent decreased efficacy of antibiotic prophylaxis
In some instances, resistance is declining. Map __.1 shows the global prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), a common skin and soft tissue infection. MRSA is decreasing in Canada, Europe, South Africa, and the United States (CDDEP n.d.; EARS-Net 2014; Public Health Agency of Canada 2015). However, steep increases have been detected in several LMICs, including India (box __.1). Resistance to last-resort antibiotics, the carbapenems, is low but increasing in Enterobacteriaceae in many LMICs (CDDEP n.d.; Lerner and others 2015). Extended-spectrum beta-lactamase producers are also increasingly prevalent worldwide, including in Africa and Latin America, while some once easily curable infections, such as *Neisseria gonorrhoea*, may be running out of available treatment options (Datta and others 2012; Lu and others 2012; PAHO n.d.; Storberg 2014).

*Source:* Teillant and others 2015
Box __.1 Antibiotic Resistance in India

India has some of the highest rates of antibiotic consumption and resistance in the world. Use is increasing alongside improved livelihoods and expanded access to drugs, with 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. Coupled with poor health infrastructure, poor-quality drugs, and a high burden of disease, India’s rates of resistant infections are on the rise.

India was the top consumer of antibiotics in 2010 and one of the top global consumers of antibiotics in agriculture. Consumption of faropenem, the only oral carbapenem currently available, 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 have high resistance to most antibiotics, including last-resort 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).

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<< map __.1 about here>>
Map 1. Percentage of *Staphylococcus aureus* Isolates That Are Methicillin Resistant (MRSA), by Country, Most Recent Year, 2011–14

*Source:* CDDEP n.d.; WHO 2014; PAHO.

*Note:* Where available, data from hospital-associated 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: oxacillin, cefoxitin, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are considered resistant in some calculations, as in the original data source.

<<end figure>>

**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 due, in part, to rising incomes and increased access to drugs. 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 increase antibiotic prescribing (Linder and others 2016, Dosh and others 2000).
Antibiotic use is also correlated with season, increasing in the winter (December–February in the
northern hemisphere and August–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 *Clostridium difficile* infection, which takes
place when antibiotic treatment has destroyed the normal gut flora and is responsible for 14,000
deaths a year in the United States (CDC 2013).

As shown on map __.2, antibiotic consumption increased more than 30 percent in 71
countries between 2000 and 2010, reaching 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 declined in some high-income countries
(HICs) from 2000 to 2010, per capita consumption in the United States is still the highest in the
world, at 22 standard units per person (map __.2). Consumption grew fastest in middle-income
countries, such as the BRICS: Brazil, Russia, India, China, and South Africa.

<<Map __.2 about here>>
Human consumption of antibiotics is often inappropriate in both LMICs and HICs, being purchased over the counter or prescribed incorrectly by a physician when antibiotics are not needed and will not be effective. Diarrheal and respiratory infections are frequently treated with antibiotics in the absence of diagnostics, even if these practices bring no benefit to patients, and both consumers and prescribers may lack awareness, education, or incentive to use antibiotics correctly.

An estimated 80 percent of all antibiotics are purchased from pharmacies, private clinics, and primary care facilities, broadly termed in the community, rather than inpatient hospital settings (Kotwani and Holloway 2011). Many of these antibiotics are purchased without a
prescription, but increased regulation is not an appropriate solution for communities who lack access to antibiotics through any other means. Changing consumption patterns in the community will require interventions that target incentives linked to consumers, prescribers and retailers.

Use in Hospitals

The volume of antibiotics used is greater in the community, but the clinical consequences of resistance are greater in hospitals, home to a rotating population of seriously ill patients treated heavily with medications, including antibiotics. Suboptimal prescribing is common in both LMICs and HICs. In Nepal, an estimated 10–40 percent of antibiotic use is inappropriate, and 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 just one-third of patients, even though 58 percent of patients tested negative for bacterial infection (Braykov and others 2014). The use of carbapenems, the last-resort antibiotic class used to treat resistant infections, is rapidly increasing in hospitals (figure ___) (CDDEP, n.d.). In some countries, China being an example, doctors or hospitals profit from the volume of antibiotics sold (Currie, Lin, and Meng 2014).

<<figure ___ about here>>

Figure ___ Per capita carbapenem use in the hospital sector, 2005-2010
Use in Food Animal Production

At least two-thirds of all antibiotics, including those that are important for human medicine, are used in livestock production at subtherapeutic levels to promote growth and prevent disease and at therapeutic levels to treat disease (Laxminarayan and others 2015). Resistant bacteria can develop in the gut of livestock or in water that has been treated with antibiotics for animal consumption. These drug-resistant bacteria can then spread to humans through direct contact with animals and infected food, water, or waste (Marshall and Levy 2011). As shown on map __3, antibiotic use in agriculture is widespread and expected to grow by more than two-thirds by 2030 (Van Boeckel and others 2015). This widespread use creates strong selection pressure, encouraging the emergence of resistance (Laxminarayan and others 2015).

<<map __3 about here>>
<<n-dash on numbers in legend>>
In many LMICs, antibiotics have long been used in place of improved sanitation and hygiene to prevent disease in intensive animal production systems. As incomes rise in LMICs, the demand for animal-source food products grows (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, the largest increase in antibiotic use for food production will occur in LMICs, with the BRICS experiencing an estimated 99 percent increase in antibiotic use in food production (Laxminarayan and others 2015). Consumption is also increasing in some HICs.

Figure _____.4 illustrates increasing antibiotic consumption in the United States, where antibiotic use per unit of meat has increased every year from 2009 to 2014 (CDDEP, n.d.).

Figure _____.4: Antimicrobial use per unit of meat in the United States, 2009-2014
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 addressing antibiotic consumption within the next two years. Plans are expected to be context specific and ideally 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 that do, they have proven successful. Progress in Ethiopia, South Africa, and Vietnam show that action plans
are both possible to formulate in LMIC settings and are urgently needed (box __.2 describes South Africa’s plan).

<<box __.2 about here>>

**Box __.2 Comprehensive National Action Plans: The Example of South Africa**

The South African National Department of Health launched a National Strategy Framework in 2014 (Government of South Africa, 2014) that adopted recommendations set by the World Health Organization (WHO) and the International Committee of the World Organization for Animal Health to curb the threat of antibiotic resistance. Key elements of the plan 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, 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 to capture trends and create evidence-based public policies. The National Strategy Framework aims to strengthen the existing surveillance system by developing an early warning system for potential 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 resistance rates in food-producing and companion animals.

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Cost-Effective Interventions

Although data on antibiotic use and resistance in LMICs is limited, new surveillance networks and laboratory strengthening programs are being established. Online databases like the Center for Disease Dynamics, Economics, and Policy’s ResistanceMap provide global trends in use.

Evidence on effective interventions is limited by the diversity of resistance drivers and long timelines required to see an impact on antibiotic resistance rates. A recent review found that the evidence base for national interventions is insufficient to inform policies (Dar and others 2015), but areas for action have clear benefits (Jamison and others 2013).

Water, Sanitation, and Hygiene

In the United States, the burden of infectious diseases declined prior to the introduction of antibiotics, largely due to improvements in water and sanitation. Many LMICs are using antibiotics as a substitute for these improvements, but drugs alone will not achieve the same reductions. Hand washing, clean water, and excreta disposal reduce diarrheal disease by 48, 17, and 36 percent, respectively (Cairncross and others 2010). Hand washing also reduces respiratory infections by at least 16 percent (Rabie and Curtis 2006).

Sanitation and water quality require expensive infrastructure, but the savings from averted disease 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 cost-effective and the most affordable intervention at US$3.35 per disability-adjusted life year (DALY) averted (Cairncross and Valdmanis 2006).
Vaccines

The potential reduction in antibiotic use due to vaccination is considerable. An estimated 11 million days of antibiotics could be spared 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 8 percent in the United States, and a universal vaccination program in Ontario, Canada, was found to reduce influenza-associated antibiotic prescribing 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 requiring hospitalization (Falsey and others 2013; McCullers 2014).

Reductions in use translate into reductions in 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 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 67 percent and infection with trimethoprim-sulfamethoxazole-resistant strains 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 S. aureus, E. coli and K. 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, but most vaccines are highly cost-effective (Maurice
and Davey 2009). In India, health care cost savings offset the cost of vaccination against the *Haemophilus influenzae* in all states (Clark and others 2013). Similarly, an assessment of cost-effectiveness in LMICs found that the 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).

**Antibiotic Stewardship and Infection Control Programs in Hospitals**

Stewardship and infection control have been proposed as the most broadly effective interventions to reduce antibiotic use in all settings (Dar and others 2015). Components of stewardship programs such as prescription audits, peer comparisons and nudging guidelines have successfully reduced antibiotic use (Meeker and others 2014, Meeker and others 2016). Hospital antibiotic stewardship programs aim to provide the right antibiotic at the right time and the right dose and have been shown to reduce antibiotic use 11–38 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 use in addition to the prevalence and spread of HCAIs. They are particularly important in LMICs, where rates of HCAIs 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 hand washing have been shown to reduce both HCAIs 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 HCAIs in LMICs indicates that these interventions would be highly effective there as
well. The cost-effectiveness of antibiotic stewardship programs depends on the prevalence of antibiotic resistance. There is extensive evidence that stewardship programs reduce 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 antibiotic prescribing 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 instance, 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 10–12 percent (Xiao and others 2013).

There are no studies directly assessing 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 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 in the United States, introduced in 2006, also 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 them at the hospital (Currie, Lin, and Meng 2014).
Reducing the Use of Antibiotics 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. While in some cases 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 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 because of potential adverse economic impact on their farm animal sector, but research shows that the impact is minimal in farming systems that are already optimized with respect to 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 .1). For instance, 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.

<<table .1 about here>>

<table>
<thead>
<tr>
<th>Country</th>
<th>Ban on antibiotic growth promoters</th>
<th>Prescription required</th>
</tr>
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<tbody>
<tr>
<td>Australia</td>
<td>No, but some AGPs banned (fluoroquinalones, avoparcin, etc)</td>
<td>Yes, most veterinary antibiotics require a prescription</td>
</tr>
<tr>
<td>Canada</td>
<td>No. Voluntary phase out notice issued in April 2014 mimicking FDA approach</td>
<td>No. Plan to strengthen veterinary oversight</td>
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developed in line with the FDA approach

<table>
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<tr>
<th>Country</th>
<th>AGPs Banned</th>
<th>Veterinary Oversight</th>
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<tbody>
<tr>
<td>Chile</td>
<td>No data</td>
<td>No data</td>
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<tr>
<td>E.U. Member States</td>
<td>Yes. All AGPs banned in 2006</td>
<td>Yes</td>
</tr>
<tr>
<td>Israel</td>
<td>No data</td>
<td>Yes</td>
</tr>
<tr>
<td>Japan</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mexico</td>
<td>Yes, AGPs banned in 2007 with exceptions (avoparcin, vancomycin, bacitracin, tylosin, virginiamycin etc)</td>
<td>Yes</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Yes, AGP use discontinued in 2011 until a veterinary oversight system can be put in place</td>
<td>Yes, veterinary oversight system in development</td>
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<tr>
<td>South Korea</td>
<td>Yes</td>
<td>Yes, veterinary oversight system in development</td>
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<tr>
<td>Turkey</td>
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<tr>
<td>United States</td>
<td>No. FDA released voluntary guidelines to withdrawal the use of medically important antibiotics as growth promoters in 2013</td>
<td>No. Under new guidance, use of medically important antibiotics will be under the oversight of licensed veterinarians.</td>
</tr>
</tbody>
</table>

Table adapted from Laxminarayan and others 2015


Evidence from HICs suggests that the economic impact of removing growth promoters is low, but this may be different in LMICs where antibiotics are still used in place of hygiene and other measures to optimize production. Little data exist about antibiotic consumption in animals or the cost-effectiveness of antibiotic bans.
Education and Awareness

Campaigns have successfully reduced the use of antibiotics in HICs, but evidence from LMICs is sparse (Huttner and others 2010). Awareness campaigns in France and Belgium reduced antibiotic prescribing 27 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 Centers for Disease Control’s Get Smart Week and the WHO Antibiotic Awareness Week (Global Antibiotic Resistance Partnership 2015).

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.

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 national surveillance programs, private sector laboratories often collect data on resistance and represent an underused resource in many areas. Laboratories are providing some of the only resistance data in countries such as India and Kenya (CDDEP n.d.).

Regional surveillance networks collect data in Latin America (ReLavra), Asia (ANSORP), Central Asia and Eastern Europe (CESAR), and Europe (EARS-Net). ResistanceMap, currently the largest 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 seven new antibiotics approved in 2014 and 37 under development (Doshi 2015; Pew Charitable Trusts 2014), but new drugs will always be needed as resistance develops.

Because all antibiotics will eventually generate resistance, alternatives to antibiotics present another treatment option. Alternatives include vaccines and improved diagnostics, as described above, 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 more than £1.5 billion ($2.1 billion USD) (Czaplewski and others 2016).

**Recommendations**

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 several key interventions to curb antibiotic resistance (figure __.5).

<<figure __.5 about here>>
The following recommendations should be part of any national plan:

- **Reduce the need for antibiotics through improved water, sanitation, and immunization.** Preventing disease achieves the dual purpose of keeping people healthy and saving antibiotic doses. Water, sanitation, hygiene, and vaccination should be core components of any public health system.

- **Improve hospital infection control and antibiotic stewardship.** Antibiotic stewardship programs, infection prevention and control, and especially hand washing with soap can reduce infections, antibiotic use, and resistance, while improving patient outcomes.

- **Adopt incentives that encourage antibiotic stewardship and discourage overuse.** Making sure that payments are not linked to prescribing, and introducing rewards for compliance may improve prescribing patterns.
• *Reduce and eventually phase out subtherapeutic antibiotic use in agriculture.* Improved sanitation and hygiene on the farm level would reduce the need for prophylactic antibiotics. Thus, antibiotic use in animal agriculture should be reduced, focusing on involving farmers and the agricultural industry in a careful phase-out of the use of growth promoters and premixed animal feeds (Laxminarayan, Van Boeckel, and Teillant 2015).

• *Educate health professionals, policy makers, and the public on sustainable antibiotic use.* Although antibiotic resistance is recognized as a problem, the same is not true of actions that can be taken to reduce use. Patients, mothers, health care providers, stakeholders, and hospital heads all need to be aware of what they can do to reduce unnecessary use.

• *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 in research, development, capacity building, and laboratory support for improved surveillance.

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Note

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.
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