

Health Policy Brief

MAY 21, 2015

Antibiotic Resistance. Because of overuse and misuse, some antibiotics are losing effectiveness against highly resistant bacteria.

WHAT'S THE ISSUE?

Many of the world's diseases are caused by microorganisms such as bacteria, fungi, viruses, and parasites. While there are a number of drugs designed to treat these infections, resistant strains are emerging at a rate that is currently outpacing the development of effective new drugs. [Methicillin-resistant *Staphylococcus aureus* \(MRSA\)](#) alone kills more than 19,000 Americans every year—more than emphysema, HIV/AIDS, Parkinson's disease, and homicide combined. Despite this public health need, pharmaceutical companies do not have strong economic incentives to develop new antibiotic drugs.

Unless new drugs are developed—together with measures taken to slow the emergence of new drug-resistant microbes—previously treatable infections will become major public health concerns, posing grave threats to infected individuals and increasing the risk of spreading to others. In recent years, several global and national public health organizations have highlighted the growing number of multidrug-resistant microbes as a major public health priority.

The commonly used term “antimicrobial resistance” applies to any microbe—bacteria, fungus, or virus—against which drugs have

declining, limited, or zero effectiveness. This policy brief primarily focuses on the diminishing effectiveness of many drugs specifically in fighting bacteria, referred to here as “antibiotic resistance.”

With so many agencies involved in the regulation and use of antibiotics, comprehensive solutions must focus on creating a coordinated plan that touches on aspects of research and development as well as enhanced infection prevention and control, and stewardship to ensure the proper use of these drugs across different settings.

This brief provides an overview of antibiotic resistance, including a summary of its current impact, the factors that contribute to its spread, and the policy recommendations put in place by federal and global public health agencies. It also reviews the debate around the regulation of antibiotic use in agriculture and examines new developments in policy and research associated with multidrug-resistant bacterial diseases and their underlying causes.

WHAT'S THE BACKGROUND?

According to the [Centers for Disease Control and Prevention](#) (CDC), at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone. In 2013 there were about 480,000 new

“The more antibiotics are used, the more opportunities bacteria have to evolve to defeat them.”

global cases of multidrug-resistant tuberculosis. According to the World Health Organization (WHO), gonorrhea may soon become untreatable as more than ten countries have reported strains that are resistant to all currently available forms of antibiotic treatment, and no new drugs have been approved. If trends persist and resistance continues to rise, some reports estimate that by 2050 there will be ten million antimicrobial resistance–related deaths worldwide, costing the world up to [US\\$100 trillion](#).

To some degree, antibiotic resistance is unavoidable. The development of resistance is an evolutionary inevitability, even where antimicrobials are used properly and sparingly. All microbes have the potential to mutate and render drugs ineffective. Once a few have mutated, they spread when antibiotics wipe out the susceptible bacteria, leaving a niche for the resistant ones to occupy.

Antibiotic-resistant infections typically occur in health care–related settings, such as hospitals and nursing homes, where infections can spread quickly between patients with compromised immune systems. Patients who use certain medical devices, such as ventilators and catheters, are at a higher risk for infection, according to the [CDC](#).

Overuse and Misuse

The more antibiotics are used, the more opportunities bacteria have to evolve to defeat them. The overuse of antibiotics—the [CDC](#) estimates that up to 50 percent of antibiotics are unnecessary or inappropriate as prescribed—in medicine and agriculture has led to a slew of so-called superbugs.

The potential impact of widespread antibiotic resistance is far reaching within the health care system. When first-line and then second-line antibiotic treatment options are limited by resistance or are unavailable, health care providers are forced to use antibiotics that may be less effective and more toxic and that may require resources such as longer hospital stays—driving up both morbidity rates and health care costs.

Without new therapies to treat or prevent infections, lifesaving procedures such as organ transplants, chemotherapy, dialysis, and caesarian sections will become more dangerous; and non-lifesaving surgeries, such as hip operations, that allow people to live active lives for longer and may enable them to stay

in the workforce could theoretically become too risky to undertake at all.

One issue that makes antibiotic resistance difficult to combat is that drug-resistant microbes are everywhere. According to the WHO, in all regions of the world there are high proportions of antibiotic resistance in bacteria that cause common infections in the urinary tract, lungs, and bloodstream; and a high percentage of hospital-acquired infections are caused by highly resistant or multi-drug-resistant bacteria. In fact, most [deaths related to antibiotic resistance](#) are attributable to infections acquired in health care settings such as hospitals and nursing homes.

Another frequently cited factor in the emergence of multidrug-resistant strains of bacteria is the misuse of antibiotics. For example when patients fail to complete their drug regimens at home, they may allow some bacteria to survive the treatment and develop resistance in the process. In other circumstances, antibiotics may be prescribed when they are not medically necessary. This can allow otherwise harmless bacteria to develop resistance, which may then be transferred to other more dangerous bacteria.

Agricultural Use

While these practices may contribute to the spread of resistant microbes, human consumption only makes up about 20 percent of antibiotic sales in the United States. The vast majority of antibiotics is used agriculturally in beef, poultry, pork, and fish farms to prevent infection and promote growth among the animals.

While it is unclear whether the larger volume of antibiotics used in agriculture compared to hospitals translates to a greater contribution to the emergence of multidrug-resistant strains of bacteria, the use of the drugs in food production has garnered a significant amount of attention in media and policy spheres.

According to an [investigative report](#) by the news outlet Reuters, [antibiotics](#) are given as standard practice during most of the life of chickens, not just when the birds are sick. In every instance of antibiotic use identified, the doses were at the low levels that scientists say are especially conducive to the development of drug-resistant strains.

Many of the antibiotics used agriculturally belong to categories considered medically im-

portant to humans (such as penicillin and tetracyclines). Despite this evidence, the United States (in sharp contrast to [Europe](#), which has a long history of restricting antibiotic use in animals) has been slow to pass any binding legislation limiting the agricultural use of critical antibiotics.

23,000 deaths

According to the CDC, at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone.

WHAT'S THE POLICY?

Combating antibiotic resistance will require coordination on behalf of a complex web of stakeholders. The National Institutes of Health funds research, including studies that pertain to the development of new antimicrobial products. The Food and Drug Administration (FDA) approves them for marketing and sale. The Department of Agriculture and the FDA have roles overseeing their agricultural use.

The CDC, in addition to its role in surveillance, prevention, and control, tracks diseases and engages in public education campaigns to inform doctors and patients how the drugs should be used in humans. The Biomedical Advanced Research and Development Authority engages the drug development industry in an integrated, systematic approach to developing and procuring drugs in tackling public health emergencies. The Department of Defense (DOD) and the Department of Veterans Affairs (VA) determine appropriate use and monitoring in military patient populations. And the State Department determines the US trade policy on prescription drugs.

In recent years, several global and federal health agencies have attempted to call attention to the issue of antibiotic resistance and, more broadly, antimicrobial resistance. In 2011 the theme of World Health Day was “Antimicrobial resistance: no action today, no cure tomorrow.” The initiative resulted in a six-point policy package designed to assist countries with tools to combat antimicrobial resistance. In summary, the points were as follows:

- To commit to a comprehensive, financed national plan with accountability and civil society engagement;
- To strengthen surveillance and laboratory capacity;
- To ensure uninterrupted access to essential medicines of assured quality;
- To regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care;

- To enhance infection prevention and control; and

- To foster innovations and research and development for new tools.

In 2012, as part of the Food and Drug Administration Safety and Innovation Act, President Barack Obama signed into law the [Generating Antibiotic Incentives Now \(GAIN\) Act of 2011](#). These provisions added a five-year extension to the exclusivity period during which antibiotics that treat serious or life-threatening infections could be sold without generic competition. The intention of the act was to increase the potential for profits from new antibiotics—giving drug companies more time to recoup their investment costs and encourage the development of new antibiotics.

In 2014 the WHO published its first global report on surveillance of antimicrobial resistance, with data provided by 114 countries. The WHO has already initiated a collaboration with partners across many sectors to identify strategies and actions to mitigate antimicrobial resistance. Those partners have included the World Organisation for Animal Health and the Food and Agriculture Organization of the United Nations to promote best practices to avoid the emergence and spread of antibacterial resistance, including optimal use of antibiotics in both humans and animals.

In January 2014 President Obama again mentioned antibiotic resistance—this time in his State of the Union address. In March 2014 he announced he would add \$30 million to the budget to fund monitoring and research into drug-resistant bacteria. Then in September 2014 he issued an executive order on combating antibiotic-resistant bacteria. In it, he called for the establishment of a “task force for combating antibiotic-resistant bacteria...to be co-chaired by the secretaries of Defense, Agriculture, and [Health and Human Services]” with the mission of creating a five-year National Action Plan that would include goals, milestones, and metrics for measuring progress.

In March 2015 President Obama urged Congress to double the federal funding available for antibiotic resistance surveillance and prevention, bringing the total to more than \$1.2 million. The same month, the White House released the [National Action Plan for Combating Antibiotic-Resistant Bacteria](#) that had been promised the previous fall. The plan detailed five goals: slowing the emergence of drug-resistant bacteria, strengthening national

“In general, new antibiotics are less profitable compared to other types of drugs.”

surveillance efforts, improving rapid diagnostic tests for resistant strains of bacteria, promoting research, and fostering collaboration.

Under each goal, the action plan lays out key milestones for the next one, three, and five years. For example, the plan calls for routine reporting of antibiotic use and resistance data by 95 percent of Medicare-eligible hospitals, as well as by DOD and VA health care facilities, by 2020. Over the same time period, the CDC and the FDA will create the repository and database for resistant bacterial strains and, in conjunction with the DOD, will provide them to diagnostic test manufacturers and research laboratories, as needed. Using these new systems, the task force has called for the reduction of inappropriate antibiotic use over the next five years by 50 percent in outpatient settings and by 20 percent in inpatient settings.

WHAT'S THE DEBATE?

Antibiotic Use in Animals

One portion of the debate surrounding antibiotic resistance has to do with its implications for animal husbandry. The WHO, the American Medical Association, the Infectious Disease Society of America, the Consumers Union, the Union of Concerned Scientists, and about 450 other organizations support legislation that would eliminate routine antibiotic use in animal feed and water.

Historically, policy attempts to regulate the use of antibiotics in animal feed have not been successful. In 2007 Rep. Louise Slaughter (D-NY) proposed a bill called the Preservation of Antibiotics for Medical Treatment Act, or PAMTA, which would require drug manufacturers to prove that the non-therapeutic use of their antibiotics wouldn't contribute to antibiotic resistance. This bill would have phased out the nontherapeutic use of antibiotics in animal feed and water, prohibit the use of antibiotics in animals that aren't sick, and make it illegal to routinely give animals antibiotics for disease prevention.

The bill was supported by medical and scientific experts and opposed by meat industry stakeholders, including the National Beef Packing Company, the National Pork Producers Council, the Animal Health Institute, the American Veterinary Medical Association, the National Chicken Council, the National Turkey Federation, the Food Marketing Institute, and several major pharmaceutical companies. The companies argued that phasing out anti-

biotics would be a major blow to the industry, resulting in sicker animals and inferior consumer products. PAMTA was introduced to Congress in 2007, 2009, 2011, and 2013. It was referred to committee multiple times but was never heard in the House Committee on Energy and Commerce.

The FDA does provide voluntary guidelines that will have the effect of regulating antibiotic use by producers of poultry, swine, beef cattle, and other livestock. The use of medically important antibiotics (as determined by the FDA) for growth promotion is scheduled to be phased out by December 2016. The FDA says it also inspects the mills where animal feed is made but does not examine the feed tickets—documents that show why the drugs are administered.

In June 2014 the FDA released a progress report on its strategy to promote the judicious use of antibiotics in food-producing animals. According to the report, all twenty-six drug manufacturers affected by the FDA's voluntary guidelines agreed to fully engage in the strategy by modifying labels so that medically important antimicrobials will not be used to promote growth. At the same time, they will incorporate the oversight of a veterinarian for the remaining therapeutic uses of such drugs.

Additionally, in November 2014 the [Pew Charitable Trusts](#) reviewed the labels of all 287 antibiotic products identified as being affected by the guidance and found that eighty-three of the labels had overlapping growth promotion and prevention dosages.

In April 2015 Tyson Foods, the largest poultry producer in the United States, announced that it would eliminate the use of human antibiotics in its flocks by September 2017.

New Drug Development

Another major branch of the debate has focused on what the government's role should be in incentivizing the development of new antibacterial drugs. In general, the direction of new pharmaceutical research by private corporations is driven, at least in part, by the expectation of return-on-investment. Companies make money on drugs when they are used in high volume, sold at a high price, or both. Developing new antibiotics—while medically necessary—does not necessarily lend itself to any of these money-making scenarios.

Antibiotics are widely used but have historically been fairly inexpensive. In recent years US antibiotic prescriptions per capita have declined compared to all prescription drugs (see Exhibit 1). In 2013 antibiotics accounted for [6.4 percent of all US prescriptions](#) but only 2.6 percent by value. This discrepancy, paired with the medical need for new antibiotics, has prompted some advocates to push for government intervention in the drug approval process specific to antibiotic development. Some policy makers have suggested allowing for higher reimbursement from insurance companies as a way to incentivize new treatments.

Another approach would be to alter the drug development pathway for antibiotics that addressed an unmet medical need. For drugs that qualify, this could reduce cost barriers to get new products to market. In 2013 the FDA held a public hearing on a potential pathway to expedite the approval of critical new drugs, including antibiotics needed to treat serious or life-threatening infections with few or no satisfactory treatment options. This Limited Population Antibacterial Drug (LPAD) approval pathway would evaluate these drugs using smaller trials than traditional drug development programs.

The streamlined LPAD pathway, while potentially innovative, may come at some cost. There would be some uncertainty about potential risks based on smaller trials that are less able to identify and predict infrequent adverse events in any statistically significant way. This is less of a concern with a limited population of patients with serious or life-threatening infections and unmet medical needs, but these risks would be of more concern if the drugs were to be used in a more general patient pop-

ulation. The medications would need to be labeled clearly for physicians so that they could effectively weigh the medications' risks and benefits as they pertain to particular patients.

Additionally, provisions in the GAIN Act referenced above help stimulate the development of new antibiotics. Under the act, certain antibacterial or antifungal drugs intended to treat serious or life-threatening infections can be designated as Qualified Infectious Disease Products (QIDPs), which receive priority review and are eligible for fast-track designation.

The act also incentivized new drug development by giving drug companies five more years of market exclusivity without generic competition. As of September 2014 the FDA had granted [fifty-nine QIDP designations](#) for thirty-nine different molecules. In February 2015 the FDA approved Avycaz, the fifth new antibacterial drug with the QIDP designation.

The GAIN Act has increased drug company interest in developing antibiotics, but some critics say it's still not enough. In a February 2015 op-ed published in the [New York Times](#), oncologist and University of Pennsylvania vice provost Ezekiel J. Emanuel suggested that the US government partner with other countries to offer a US\$2 billion prize to the first five companies or academic institutions to develop and get regulatory approval for a new class of antibiotics. He reasoned that the payment would provide a beneficial return for companies, as well as provide cost savings for the health care system, which he estimated spends about US\$20 billion per year on costs related to antibiotic resistance.

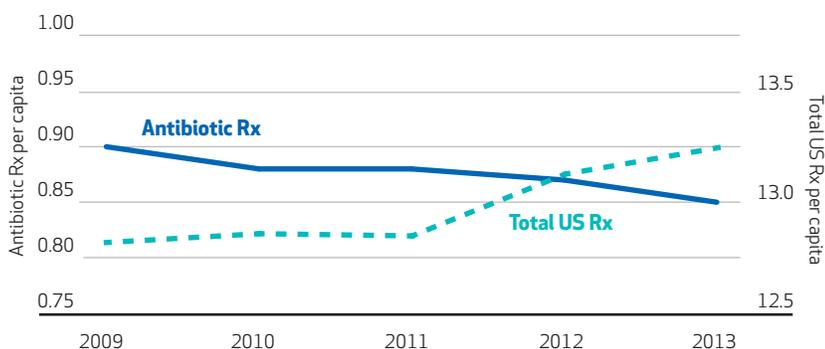
A [recent report](#) released from the UK's Review on Antimicrobial Resistance (AMR) looks specifically at ways to encourage and improve the development of new antibiotic drugs. The report recommends creating a global AMR Innovation Fund to boost investment in early-stage research and "de-link" a drug's profit from its volume in sales.

Other Policy Proposals

Within health care settings and medical practices, efforts to stem antibiotic resistance have focused on more judicious prescribing policies and infection control. In 2013 the [CDC](#) estimated that four out of five Americans are prescribed antibiotics each year. Part of this is as a result of physicians' prescribing anti-

EXHIBIT 1

Per Capita US Prescriptions, Antibiotic and Total, 2009–13



SOURCE Kevin Utterson, John H. Powers, Gregory W. Daniel, and Mark B. McClellan, "Repairing the Broken Market for Antibiotic Innovation," *Health Affairs* 34, no. 2 (2015):277–85.

50% of antibiotics

The CDC estimates that up to 50 percent of antibiotics are unnecessary or inappropriate as prescribed.

biotics defensively, even if their patients most likely will not benefit from them.

Options for curbing this practice have included incentive payments and feedback systems, but these programs can be expensive and have had limited success. One technique that has shown some promise is to educate patients about the proper use and prescription of antibiotics. A [2014 study](#) found that a simply worded poster placed in exam rooms helped reduce unnecessary antibiotic prescriptions for respiratory infections during flu season by approximately 20 percent.

It is not just prescription drugs that have come under stricter scrutiny. In May 2015 the [FDA proposed a rule](#) that would require companies that manufacture hand sanitizers used in hospital settings to submit new studies looking at key safety issues, including possible hormonal effects and contributions to antibiotic-resistant bacteria. Products that could not be proven safe and effective by 2018 would have to be reformulated or removed from the market.

WHAT'S NEXT?

There are several potential directions for new antimicrobial drug research and development. Better diagnostic tools could affect the way antibiotic resistance is detected, diagnosed, and reported. More rapid tests could help to prevent overprescription of antibiotics and assist with global surveillance measures already emerging as a result of policy goals.

There are also potential developments for new drugs. Researchers at Northeastern University recently published a paper in *Nature* about a potential new antibiotic called

teixobactin that targets polymers that build the bacterial cell wall. The drug's pathway—examined in mice but not yet in humans—is similar to vancomycin, another antibiotic often used as a last-resort treatment for resistant strains of bacteria such as MRSA. In their paper, the researchers highlighted how the technology used for this discovery might help lead to additional drug discoveries.

While it is tempting to assume that a potential new human antibiotic means that the pharmaceutical industry's interest in developing new antibacterial drugs will spring back into gear, it's important to consider that the failure rate for antibiotics from early discovery stage to actual drug approval is [97 percent](#). In general, new antibiotics are less profitable compared to other types of drugs, as their use is tightly controlled by hospitals trying to prevent the emergence of new resistant strains, and yet drug companies are not able to compensate for slow adoption by charging more because they'd have to compete with inexpensive generic antibiotics. In 2011, for example, Pfizer, one of the few drug companies to work on developing new antibiotics, closed its research lab in Connecticut.

For health care facilities, life science researchers, federal agencies, and local health officials to meet many of the specific goals outlined in the Obama administration's recent National Action Plan, they will require additional resources. To that end, President Obama's fiscal year 2016 budget proposes to nearly double the amount of federal funding for combating and preventing antibiotic resistance to more than \$1.2 billion. Congress, however, is unlikely to support and enact the president's full budget request. ■

About Health Policy Briefs

Written by
Teresa Chin
Consulting Editor

Editorial review by
Robert Guidos
Senior Advisor to the Director
Center for Drug Evaluation and Research
Food and Drug Administration

Kevin Outtersson
Professor of Law and N. Neal Pike Scholar
in Health and Disability Law
Boston University
Associate Fellow, Chatham House
Editor in Chief, *Journal of Law,
Medicine and Ethics*

Rachel Zetts
Senior Associate, Antibiotic Resistance
Project
Pew Charitable Trusts

Rob Lott
Deputy Editor
Health Affairs

Tracy Gnadinger
Assistant Editor
Health Affairs

Health Policy Briefs are produced under
a partnership of *Health Affairs* and the
Robert Wood Johnson Foundation.

Cite as:
"Health Policy Brief: Antibiotic
Resistance," *Health Affairs*,
May 21, 2015.

Sign up for free policy briefs at:
[www.healthaffairs.org/
healthpolicybriefs](http://www.healthaffairs.org/healthpolicybriefs)

RESOURCES

Antibiotic Resistance Project, *GAIN: How a New Law Is Stimulating the Development of Antibiotics* (Philadelphia, PA: Pew Charitable Trusts, November 7, 2013).

Antibiotic Resistance Project, *Gaps in FDA's Antibiotics Policy* (Philadelphia, PA: Pew Charitable Trusts, November 30, 2014).

Carol Cogliani, Herman Goossens, and Christina Greko, "[Restricting Antimicrobial Use in Food Animals: Lessons from Europe](#)," *Microbe* 6, no. 6 (2011): 274–9.

Nadine Czekalski, Tom Berthold, Serena Caucci, Andrea Egli, and Helmut Bürgmann, "[Increased Levels of Multiresistant Bacteria and Resistance Genes after Wastewater Treatment and Their Dissemination into Lake Geneva, Switzerland](#)," *Frontiers in Microbiology* 3 (2012):106.

Michael A. Jahne, Shane W. Rogers, Ivan P. Rambler, Edith Holder, and Gina Hayes, "[Hierarchical Clustering Yields Insight into Multidrug-Resistant Bacteria Isolated from a Cattle Feedlot Wastewater Treatment System](#)," *Environmental Monitoring and Assessment* 187, no. 1 (2015): 4168.

Timothy F. Landers, Bevin Cohen, Thomas E. Wittum, and Elaine L. Larson, "[A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential](#)," *Public Health Reports* 127, no. 1 (2012): 4–22.

Losee L. Ling, Tanja Schneider, Aaron J. Peoples, et al., "[A New Antibiotic Kills Pathogens without Detectable Resistance](#)," *Nature* 517 (2015): 455–9.

Review on Antimicrobial Resistance, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations* (London, UK: Review on Antimicrobial Resistance, December 2014).

Brad Spellberg, Martin Blaser, Robert J. Guidos, et al., "[Combating Antimicrobial Resistance: Policy Recommendations to Save Lives](#)," *Clinical Infectious Diseases* 52, Suppl 5 (2011): S397–428.

The White House, *Executive Order—Combating Antibiotic-Resistant Bacteria* (Washington, DC: White House Press Office, September 18, 2014).

World Health Organization, *Antimicrobial Resistance* (Geneva, Switzerland: World Health Organization, updated April 2015).