Antibiotic Resistance: A Human Health Perspective

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More than one hundred years ago, Dr. Paul Ehrlich coined the term "magic bullet" to describe a highly targeted chemical treatment that could eradicate an infection. Intravenous penicillin first used clinically in 1941, established antibiotics as the foundation for modern medicine. Cancer treatment, transplants, renal dialysis, and virtually the entire armamentarium of life-saving treatments are dependent on the ability to treat infections with antibiotics. Today, however, medical practitioners, scientists, government officials, and private sector industries are all dealing with the growing threat of antimicrobial resistance (AMR) and the potential emergence of a post-antibiotic era—a period of untreatable bacterial infections not seen since the early 20th Century.[1] In addressing antibiotic resistance, we need to accept that no magic bullet— no single targeted intervention or strategy—exists that will effectively prevent and control AMR. Because the factors driving the AMR crisis are so diverse, and our understanding of these factors is still evolving, we will need to develop strategies that tackle each component of the problem without losing sight of the broader context of widespread antibiotic use and the spread of resistant bacteria.

AMR basics for the 21st Century

Sustainable solutions to the AMR problem are required because the "arms race" between human efforts to find magic bullets to treat specific infectious diseases and the ability of bacteria to evolve resistance is permanent. Although better prevention, new vaccines, and non-antibiotic therapies may eventually play an important role in human and animal health, antibiotics will always be needed to treat infections, and the likelihood of ever developing an antibiotic to which some bacteria will not evolve resistance is exceedingly remote.[2]

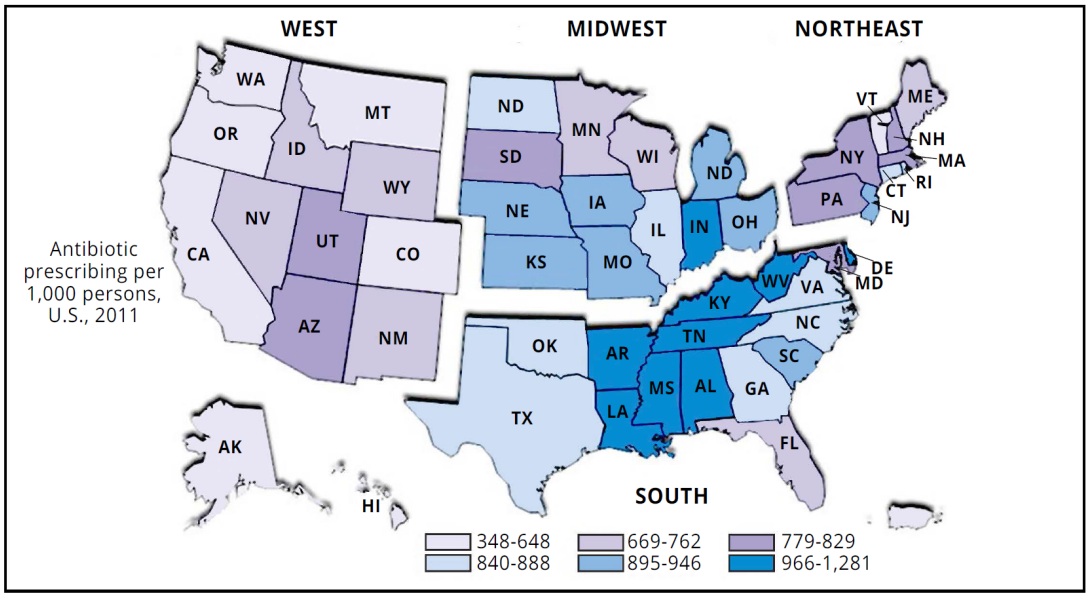

Figure 1. Adapted from Hicks, L. A., et al., 2015. US Outpatient Antibiotic Prescribing Variation According to Geography, Patient Population, and Provider Specialty in 2011. Clin Infect Dis 60(9):1308-1316.

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The use of antibiotics, at any time, in any setting, drives antibiotic resistance. When large populations of bacteria are exposed to antibiotics, some of those bacteria will mutate in ways that enable them to survive and reproduce while susceptible bacteria are inhibited or killed, allowing the resistant bacteria to become more prominent and more likely to spread. This is true whether the bacteria encounter antibiotics in the intestinal tract of a person or an animal, in sewage runoff, or anywhere in the animate or inanimate environment.[1,3] What is not well understood at present are the complex dynamics that connect the microbiology of resistance (the way the bacteria mutate and share resistance genes) and the epidemiology of resistance (the way people and animals transmit resistant bacteria within and across species), resulting in the spread of bacterial resistance within communities and around the world. In 2013, the Centers for Disease Control (CDC) published a list of the drug-resistant bacteria having the greatest public health impact, identifying three as being of urgent concern, including carbapenem-resistant *Enterobacteriaceae* (CRE), which has been called the "nightmare bacteria" (Table1). Increasingly resistant forms of CRE continue to spread globally at a very rapid pace: first the KPC type (*Klebsiella pneumoniae* carbapenemase) starting in 2001, then the NDM type (New Delhi Metallo-beta-lactamase) in 2010. Both KPC and NDM are enzymes that break down carbapenems making them ineffectual. The mcr-1 type, first identified in 2015, is resistant to the only remaining available form of treatment.[1,4,5]

Table 1.
Urgent Threats
Clostridium difficile (CDIFF)
Carbapenem-resistant *Enterobacteriaceae* (CRE)
Serious Threats
Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida* (a fungus)
Extended spectrum β-lactamase producing *Enterobacteriaceae* (ESBL)
Vancomycin-resistant *Enterococcus* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant Non-typhoidal *Salmonella*
Drug-resistant *Salmonella Typhi*
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant *Streptococcus pneumoniae*
Drug-resistant tuberculosis
Concerning Threats
Vancomycin-resistant *Staphylococcus aureus* (VRSA)
Erythromycin-resistant Group A *Streptococcus*
Clindamycin-resistant Group B *Streptococcus*
Adapted from: http://www.cdc.gov/drugresistance/biggest_threats.html

In human medicine, the two basic priorities for controlling antibiotic resistance are: improving the use of antibiotics—the practice of antibiotic stewardship— by ensuring that antibiotics are prescribed in the most appropriate way and only when truly necessary, and preventing the spread of antibiotic-resistant bacteria particularly within and between healthcare institutions, but also within communities among people who haven't been in the hospital.

The fact that doctors overprescribe antibiotics has been known for decades. Despite years of educational campaigns and outreach efforts both to healthcare providers and patients, the most recent studies have shown that still, about 30% of outpatient antibiotic prescribing is inappropriate and probably unnecessary.[6] Further complicating the search for solutions is the tremendous variation in the rate at which doctors prescribe outpatient antibiotics from state to state within the United States. In high-prescribing states, patients are more than three times as likely to receive an antibiotic prescription at the doctor's office than in low-prescribing states.[7] (Figure 1).

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To date, interventions to slow the spread of antibiotic-resistant bacteria within healthcare facilities, between facilities and from healthcare institutions into the community have had limited success. Finding more effective interventions to control the spread of resistance is an important research priority, recently receiving an unprecedented level of funding for work coordinated by both the National Institutes of Health (NIH) and the CDC.8 The CDC has proposed a new community-wide strategy for the prevention and control of resistance, which it estimates could prevent 37,000 deaths over five years if fully implemented in the United States.[9]

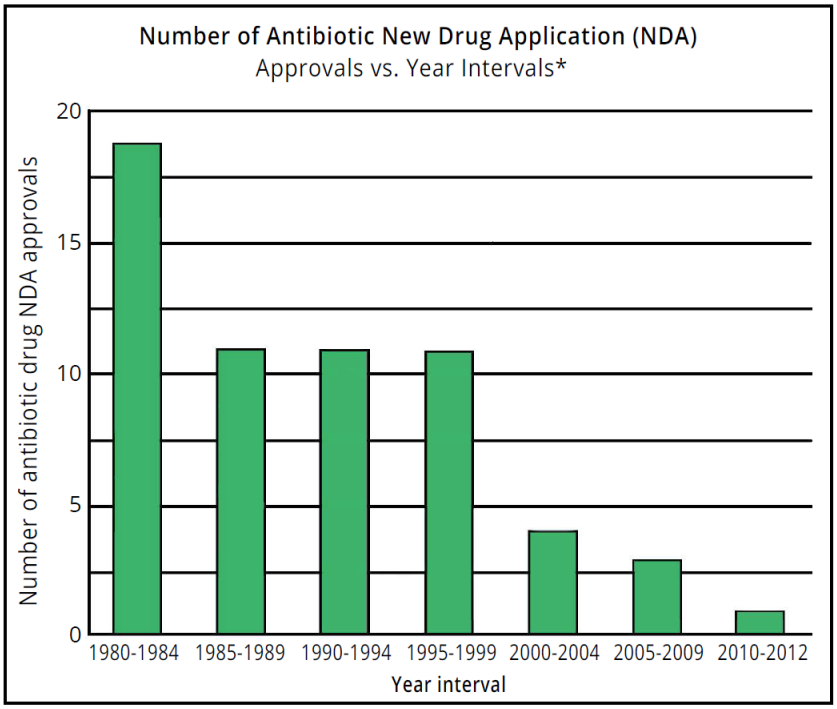

Figure 2. Adapted from https://www.cdc.gov/drugresistance/pdf/11-2013-508.pdf

*Intervals from 1980-2009 are 5-year intervals; 2010-2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

New antibiotic development has fallen off dramatically in recent decades (Figure 2). The most obvious vulnerabilities of bacteria to small-molecule chemicals—the magic bullets that Paul Ehrlich envisioned—have already been exploited. Furthermore, the economics of the pharmaceutical industry and the healthcare industry are quite different in the 21st century than they were in the mid-20th century, the so-called "golden age" of antibiotic research. The return on investment for finding, testing, and successfully marketing new antibiotics has proven insufficient to stimulate a vigorous antibiotic pipeline over the past 40 years.[10] Both the United States and the European Union have undertaken initiatives to restock that pipeline; the long-term success of those efforts will be seen over time.

The last century saw history's most dramatic improvements in medical care and health, fueled to a great degree by the development and widespread use of antibiotics. However, in the conflict between bacterial evolution and human ingenuity, many reports suggest that in this century, the bacteria seem to have gained the advantage. Maintaining our dominance over bacterial infections will require more than just the application of scientific advances in fields like microbiology, bacterial and human genomics, biochemistry and information technology. We will need the broadest societal engagement and an acceptance of the need both to rethink how antibiotics are used and to create effective global partnerships since drug-resistant bacteria have no respect for national boundaries. No simple or magical solutions exist, and the necessary changes in beliefs, attitudes and practices can only be achieved with sustained effort and open, transparent communication.

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References

[1]Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

[2]Review on AMR. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations, 2016. http://amrreview.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

[3]Finley, R. L., et al. 2013. The scourge of antibiotic resistance: the important role of the environment. Clin Infect Dis 57(5):704-710.

[4]Moellering, R. C., Jr. 2010. NDM-1--a cause for worldwide concern. N Engl J Med 363(25):2377 2379.

[5]Nordmann, P. and L. Poirel. 2016. Plasmid-mediated colistin resistance: an additional antibiotic resistance menace. Clin Microbiol Infect 22(5):398-400.

[6]Fleming-Dutra, K. E., et al. 2016. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. J Am Med Assoc 315(17):1864-1873.

[7]Hicks, L. A., et al. 2015. US Outpatient Antibiotic Prescribing Variation According to Geography, Patient Population, and Provider Specialty in 2011. Clin Infect Dis 60(9):1308-1316.

[8]Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria. 2016. http://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf

[9]CDC. Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic Resistant Infections in Health Care Facilities — United States. MMWR 2015:64(30);826-831.

[10]Harbarth, S., et al. 2015. Antibiotic research and development: business as usual? J Antimicrob Chemother 70(6):1604-1607.

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