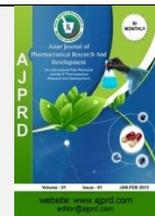


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Review Article

The Antibiotic Resistance Crisis

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ABSTRACT

Numerous deaths from infectious diseases have raised public awareness of their dangers, promoting global antimicrobial research. However, antibiotic demand and use, on the other hand, have increased antibiotic levels in natural ecosystems. Natural selection and adaptation induced antibiotic resistance gene mutations in bacterial populations. Dissemination of antibiotic resistance genes in ecosystems resulted in the emergence of antibiotic-resistant bacteria, leading to a variety of antibiotic-resistant diseases on a global scale. This review paper provides an overview of the antibiotic discovery history, antibiotic screening techniques, and industrial antibiotic production processes. In addition, the emergence of antibiotic-resistant microorganisms and the antibiotics' impact on the environment have been reviewed, and suggestions were given. The ecological perspective on antibiotic resistance has also been discussed. New drug development seems to be the prime requisite now to control microbes that no longer respond to the drug.

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INTRODUCTION

The rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives.¹⁻⁶ Many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat.⁷ The antibiotic resistance crisis has been attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements.^{2-5,8-15} The Centers for Disease Control and Prevention (CDC) has classified a number of bacteria as presenting urgent, serious, and concerning threats, many of which are already responsible for placing a substantial clinical and financial burden on the U.S. health care system, patients, and their families.^{1,5,11,16} Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.^{2,7}

THE HISTORY AND BENEFITS OF ANTIBIOTICS

History of Antibiotics

The management of microbial infections in ancient Egypt, Greece, and China is well-documented.⁴ The modern era of antibiotics started with the discovery of penicillin by Sir Alexander Fleming in 1928.^{4,13} Since then, antibiotics have transformed modern medicine and saved millions of lives.^{2,5} Antibiotics were first prescribed to treat serious infections in the 1940s.⁵ Penicillin was successful in controlling bacterial infections among World War II soldiers.⁴ However, shortly thereafter, penicillin resistance became a substantial clinical problem, so that, by the 1950s, many of the advances of the prior decade were threatened.⁷ In response, new beta-lactam antibiotics were discovered, developed, and deployed, restoring confidence.^{4,7} However, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified during that same decade, in the United Kingdom in 1962 and in the United States in 1968.^{4,5}

Unfortunately, resistance has eventually been seen to nearly all antibiotics that have been developed (Figure 1).⁵ Vancomycin was introduced into clinical practice in 1972 for the treatment of methicillin resistance in both *S. aureus* and coagulase-negative staphylococci.^{4,5} It had been so difficult to induce vancomycin resistance that it was believed unlikely to occur in a clinical setting.⁴ However, cases of vancomycin resistance were reported in coagulase-

negative staphylococci in 1979 and 1983.⁴ From the late 1960s through the early 1980s, the pharmaceutical industry introduced many new antibiotics to solve the resistance problem, but after that the antibiotic pipeline began to dry up and fewer new drugs were introduced.⁷ As a result, in 2015, many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat.⁷

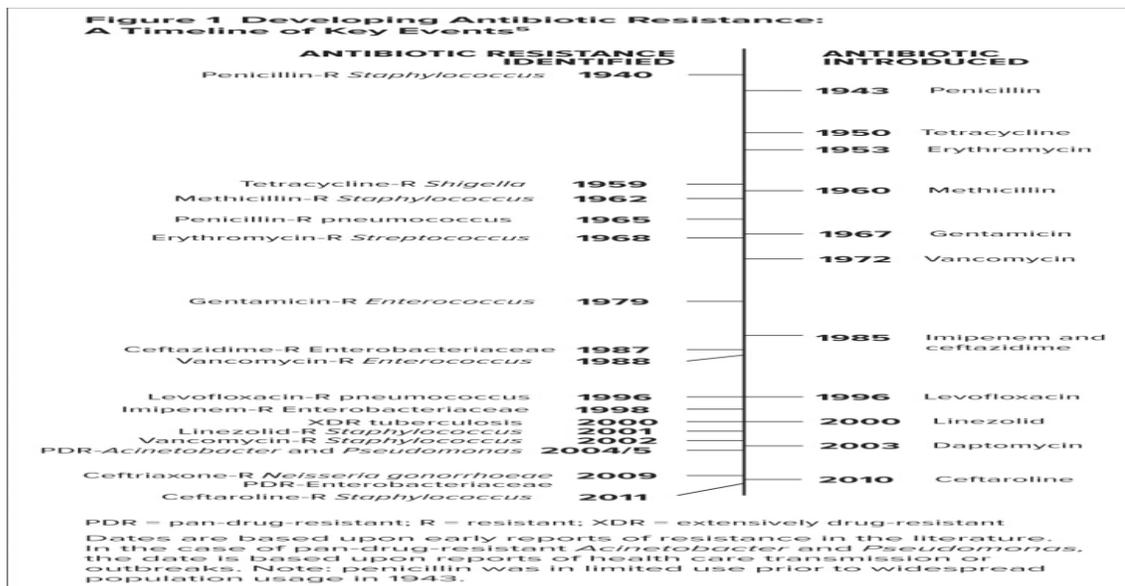


Figure 1 Developing Antibiotic Resistance: A Timeline of Key Events

PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant

Dates are based upon early reports of resistance in the literature. In the case of pan-drug-resistant *Acinetobacter* and *Pseudomonas*, the date is based upon reports of health care transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.

Benefits of Antibiotics

Antibiotics have not only saved patients' lives, they have played a pivotal role in achieving major advances in medicine and surgery.² They have successfully prevented or treated infections that can occur in patients who are receiving chemotherapy treatments; who have chronic diseases such as diabetes, end-stage renal disease, or rheumatoid arthritis; or who have had complex surgeries such as organ transplants, joint replacements, or cardiac surgery.^{2,3,5,16}

Antibiotics have also helped to extend expected life spans by changing the outcome of bacterial infections.^{13,16} In 1920, people in the U.S. were expected to live to be only 56.4 years old; now, however, the average U.S. life span is nearly 80 years.⁶ Antibiotics have had similar beneficial effects worldwide. In developing countries where sanitation is still poor, antibiotics decrease the morbidity and mortality caused by food-borne and other poverty-related infections.¹⁶

CAUSES OF THE ANTIBIOTIC RESISTANCE CRISIS

Overuse

As early as 1945, Sir Alexander Fleming raised the alarm regarding antibiotic overuse when he warned that the "public will demand [the drug and] ... then will begin an era ... of abuses."^{7,14} The overuse of antibiotics clearly drives the evolution of resistance.^{5,9} Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains.¹⁰ In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on mobile genetic elements such as plasmids.⁹ This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria.⁹ Resistance can also occur spontaneously through mutation.⁹ Antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind to reproduce as a result of natural selection.⁹ Despite warnings regarding overuse, antibiotics are overprescribed worldwide.¹⁰

In the U.S., the sheer number of antibiotics prescribed indicates that a lot of work must be done to reduce the use of these medications.¹² An analysis of the IMS Health Midas database, which estimates antibiotic consumption based on the volume of antibiotics sold in retail and hospital pharmacies, indicated that in 2010, 22.0 standard units (a unit equaling one dose, i.e., one pill, capsule, or ampoule) of antibiotics were prescribed per person in the U.S.¹⁷ The number of antibiotic prescriptions varies by state, with the most written in states running from the Great Lakes down to the Gulf Coast, whereas the West Coast has the lowest use

(Figure 2).^{5,12} In some states, the number of prescribed courses of treatment with antibiotics per year exceed the

population, amounting to more than one treatment per person per year.¹²

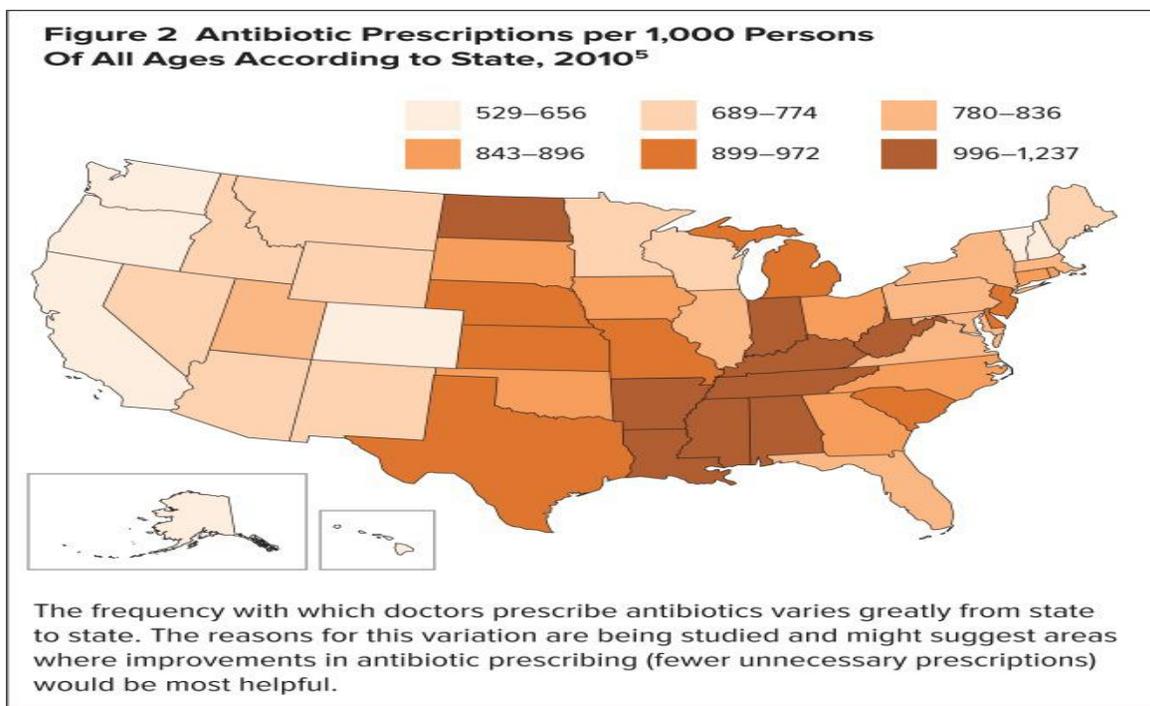


Figure 2: Antibiotic Prescriptions per 1,000 Persons of All Ages According to State, 2010⁵

The frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (fewer unnecessary prescriptions) would be most helpful.

In many other countries, antibiotics are unregulated and available over the counter without a prescription.^{10,15} This lack of regulation results in antibiotics that are easily accessible, plentiful, and cheap, which promotes overuse.¹⁵ The ability to purchase such products online has also made them accessible in countries where antibiotics are regulated.¹⁵

INAPPROPRIATE PRESCRIBING

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria.⁵ Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases.^{5,18} One U.S. study reported that a pathogen was defined in only 7.6% of 17,435 patients hospitalized with community-acquired pneumonia (CAP).¹⁴ In comparison, investigators at the Karolinska Institute in Sweden were able to identify the probable pathogen in 89% of patients with CAP through use of molecular diagnostic techniques (polymerase chain reaction [PCR] and semiquantitative PCR).¹⁴ In addition, 30% to 60% of the antibiotics prescribed in intensive care units (ICUs) have been found to be unnecessary, inappropriate, or suboptimal.¹⁸

Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy.¹¹ Subinhibitory and subtherapeutic antibiotic concentrations can promote the development of antibiotic resistance by supporting genetic

alterations, such as changes in gene expression, HGT, and mutagenesis.⁸ Changes in antibiotic-induced gene expression can increase virulence, while increased mutagenesis and HGT promote antibiotic resistance and spread.⁸ Low levels of antibiotics have been shown to contribute to strain diversification in organisms such as *Pseudomonas aeruginosa*.⁸ Subinhibitory concentrations of piperacillin and/or tazobactam have also been shown to induce broad proteomic alterations in *Bacteroides fragilis*.⁸

Extensive Agricultural Use

In both the developed and developing world, antibiotics are widely used as growth supplements in livestock.^{5,10,14} An estimated 80% of antibiotics sold in the U.S. are used in animals, primarily to promote growth and to prevent infection.^{7,12,14} Treating livestock with antimicrobials is said to improve the overall health of the animals, producing larger yields and a higher-quality product.¹⁵

The antibiotics used in livestock are ingested by humans when they consume food.¹ The transfer of resistant bacteria to humans by farm animals was first noted more than 35 years ago, when high rates of antibiotic resistance were found in the intestinal flora of both farm animals and farmers.¹⁴ More recently, molecular detection methods have demonstrated that resistant bacteria in farm animals reach consumers through meat products.¹⁴ This occurs through the following sequence of events: 1) antibiotic use in food-producing animals kills or suppresses susceptible bacteria, allowing antibiotic-resistant bacteria to thrive; 2) resistant bacteria are transmitted to humans through the food supply; 3) these bacteria can cause infections in humans that may lead to adverse health consequences.⁵

The agricultural use of antibiotics also affects the environmental microbiome.^{5,14} Up to 90% of the antibiotics given to livestock are excreted in urine and stool, then widely dispersed through fertilizer, groundwater, and surface runoff.^{5,14} In addition, tetracyclines and streptomycin are sprayed on fruit trees to act as pesticides in the western and southern U.S.¹ While this application accounts for a much smaller proportion of overall antibiotic use, the resultant geographical spread can be considerable.¹ This practice also contributes to the exposure of microorganisms in the environment to growth-inhibiting agents, altering the environmental ecology by increasing the proportion of resistant versus susceptible microorganisms.¹

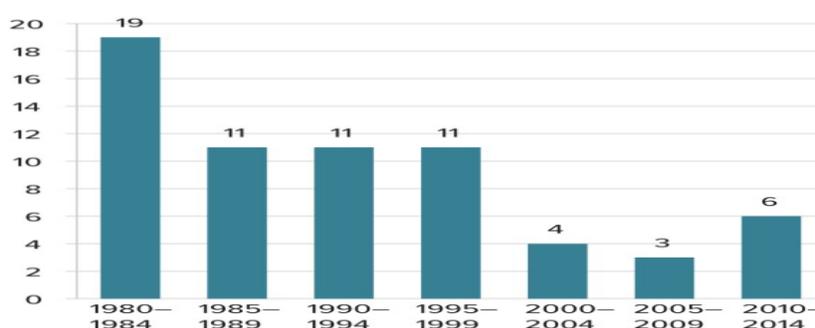
Antibacterial products sold for hygienic or cleaning purposes may also contribute to this problem, since they may limit the development of immunities to environmental

antigens in both children and adults.^{1,15} Consequently, immune-system versatility may be compromised, possibly increasing morbidity and mortality due to infections that wouldn't normally be virulent.¹⁵

AVAILABILITY OF FEW NEW ANTIBIOTICS

The development of new antibiotics by the pharmaceutical industry, a strategy that had been effective at combating resistant bacteria in the past, had essentially stalled due to economic and regulatory obstacles (Figure 3).¹⁴ Of the 18 largest pharmaceutical companies, 15 abandoned the antibiotic field.¹⁴ Mergers between pharmaceutical companies have also substantially reduced the number and diversity of research teams.¹³ Antibiotic research conducted in academia has been scaled back as a result of funding cuts due to the economic crisis.¹³

Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria.

* Drugs are limited to systemic agents. Data courtesy of the CDC⁵ and the FDA Center for Drug Evaluation and Research.

Figure 3: Number of Antibacterial New Drug Application Approvals Versus Year Intervals

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* Drugs are limited to systemic agents. Data courtesy of the CDC⁵ and the FDA Center for Drug Evaluation and Research.

Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry.¹⁴ Because antibiotics are used for relatively short periods and are often curative, antibiotics are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux.^{1-3,13,14} A cost-benefit analysis by the Office of Health Economics in London calculated that the net present value (NPV) of a new antibiotic is only about \$50 million, compared to approximately \$1 billion for a drug used to treat a neuromuscular disease.¹⁴ Because medicines for chronic conditions are more profitable, pharmaceutical companies prefer to invest in them.²

Another factor that causes antibiotic development to lack economic appeal is the relatively low cost of antibiotics. Newer antibiotics are generally priced at a maximum of \$1,000 to \$3,000 per course compared with cancer chemotherapy that costs tens of thousands of

dollars.^{2,3,13,14} The availability, ease of use, and generally low cost of antibiotics has also led to a perception of low value among payers and the public.¹³

In addition, microbiologists and infectious-disease specialists have advised restraint regarding antibiotic use.¹³ Therefore, once a new antibiotic is marketed, physicians—rather than prescribing it immediately—often hold this new agent in reserve for only the worst cases due to fear of promoting drug resistance, and they continue to prescribe older agents that have shown comparable efficacy.^{1,2} Therefore, new antibiotics are often treated as “last-line” drugs to combat serious illnesses.^{1,2} This practice leads to the reduced use of new antibiotics and a diminished return on investment.¹³

When new agents are eventually used, the emergence of resistance is nearly inevitable.² However, since bacterial evolution is uncertain, the timeline for the development of resistance is unpredictable.² A manufacturer that invests large sums of money into antibiotic development may therefore discover that profits are prematurely curtailed when resistance develops to a new antibiotic.² Economic uncertainty related to the Great Recession has also had a restraining effect on the end users of antibiotics.² Developed countries with well-funded health care systems have applied austerity measures, while developing countries such as

China and India still have a large cohort of population that cannot afford expensive new medicines.² As an additional complication, most antibiotics are currently off-patent and are supplied by manufacturers of generic drugs.³ The result has been access to cheap and generally effective drugs, which is good for the public; however, the downside is that many payers expect all antibiotics to be priced similarly—even new agents that target multidrug-resistant (MDR) pathogens.³

Because of these factors, many large pharmaceutical companies fear a potential lack of return on the millions of U.S. dollars that would be required to develop a new antibiotic.^{1,2,13} The Infectious Diseases Society of America (IDSA) reported that as of 2013, few antibacterial compounds were in phase 2 or 3 development.^{11,14} In particular, the IDSA noted that unacceptably few agents with activity against emerging, extensively resistant gram-negative bacteria, such as Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, were being developed.¹¹ Pharmaceutical companies have also taken a more active interest in developing antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA), rather than gram-negative pathogens.² The most likely explanation for this imbalance is that MRSA is a major problem worldwide, whereas the market for treating gram-negative organisms is smaller, and somewhat more unpredictable given that resistance is rapidly acquired.²

REGULATORY BARRIERS

Even for those companies that are optimistic about pursuing the discovery of new antibiotics, obtaining regulatory approval is often an obstacle.^{2,13} Between 1983 and 2007, a substantial reduction occurred in the number of new antibiotic approvals.² Difficulties in pursuing regulatory approval that have been noted include: bureaucracy, absence of clarity, differences in clinical trial requirements among countries, changes in regulatory and licensing rules, and ineffective channels of communication.¹³

Changes in standards for clinical trial design made by the U.S. Food and Drug Administration (FDA) during the past two decades have made antibiotic clinical trials particularly challenging.³ Studies comparing antibiotics with placebo are considered to be unethical; therefore, trials are designed to demonstrate noninferiority of new agents compared to existing drugs, within a varying statistical margin.³ This requires a large sample population and consequently high costs, making the development of antibiotics uneconomical and unattractive.^{3,13} While small companies have stepped in to fill the gap in antibiotic discovery and development formerly occupied by large pharmaceutical companies, the complexity and high cost of phase 3 clinical trials can exceed the financial means of these companies.¹³ However, in December 2014, Merck acquired the small antibiotic research company Cubist Pharmaceuticals, which is expected to accelerate the study and regulatory approval of new antibiotic agents in the future.¹⁹

Shlaes and Moellering have discussed how altering the requirements for trial designs can have a significant impact on the size, and hence cost, of conducting clinical trials.² Although more work in this area needs to be done, the FDA issued guidance in 2013 that changed the required

clinical trial for acute bacterial skin and skin-structure infections.²⁰ These changes included new disease state and endpoint definitions, a schedule for assessing endpoints, guidance on patient inclusion and exclusion, as well as supportive evidence and statistical justification for proposed noninferiority margins.²⁰ Although still in draft form, the updated guidelines have been adopted in some clinical trials and serve as a basis for discussions regarding further study-protocol improvements.²⁰

Additional new regulatory approaches are needed to ensure the continued development and availability of antibiotic medications.² The IDSA has proposed a new, limited-population antibiotic drug (LPAD) regulatory approval pathway that has drawn positive public comments from FDA officials.¹⁴ This model would enable substantially smaller, less-expensive, and faster clinical trials.¹⁴ In return for regulatory approval based on smaller clinical trials, the antibiotic would receive a very narrow indication focused only on the high-risk patients for whom benefits were shown to outweigh risks.¹⁴ Such limited approvals already exist in other situations, such as orphan drugs for the treatment of rare diseases.^{2,13}

ANTIBIOTIC-RESISTANT BACTERIAL INFECTIONS

Antibiotic-resistant infections are already widespread in the U.S. and across the globe.¹ A 2011 national survey of infectious-disease specialists, conducted by the IDSA Emerging Infections Network, found that more than 60% of participants had seen a pan-resistant, untreatable bacterial infection within the prior year.⁷ Many public health organizations have described the rapid emergence of resistant bacteria as a “crisis” or “nightmare scenario” that could have “catastrophic consequences.”⁸ The CDC declared in 2013 that the human race is now in the “post-antibiotic era,” and in 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming dire.¹⁵ MDR bacteria have been declared a substantial threat to U.S. public health and national security by the IDSA and the Institute of Medicine, as well as the federal Interagency Task Force on Antimicrobial Resistance.¹

Among gram-positive pathogens, a global pandemic of resistant *S. aureus* and Enterococcus species currently poses the biggest threat.^{5,16} MRSA kills more Americans each year than HIV/AIDS, Parkinson’s disease, emphysema, and homicide combined.^{1,12} Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics.¹ The global spread of drug resistance among common respiratory pathogens, including *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, is epidemic.¹⁶

Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era.^{1,5,16} The emergence of MDR (and increasingly pan-resistant) gram-negative bacilli has affected practice in every field of medicine.¹ The most serious gram-negative infections occur in health care settings and are most commonly caused by Enterobacteriaceae (mostly *Klebsiella*

pneumoniae), *Pseudomonas aeruginosa*, and *Acinetobacter*.^{5,16} MDR gram-negative pathogens are also becoming increasingly prevalent in the community.¹⁶ These include extended-spectrum beta-lactamase-producing *Escherichia coli* and *Neisseria gonorrhoeae*.¹⁶

The CDC assessed antibiotic-resistant bacterial infections according to seven factors: clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and

barriers to prevention.⁵ The threat level of each bacteria was then classified as “urgent,” “serious,” or “concerning” (Table 1).¹⁶ In general, threats that are urgent or serious require more monitoring and prevention activities, whereas those considered concerning require less.⁵ A summary of information regarding the resistant bacteria mentioned above follows. Information regarding other strains of resistant bacteria that have been identified as threats by the CDC can be found at <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>.⁵

Table 1: CDC Assessment of Antibacterial Resistance Threats 5

<p>Urgent Threats</p> <ul style="list-style-type: none"> • Clostridium difficile • Carbapenem-resistant Enterobacteriaceae (CRE) • Drug-resistant <i>Neisseria gonorrhoeae</i>
<p>Serious Threats</p> <ul style="list-style-type: none"> • Multidrug-resistant <i>Acinetobacter</i> • Drug-resistant <i>Campylobacter</i> • Fluconazole-resistant <i>Candida</i> (a fungus) • Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs) • Vancomycin-resistant Enterococci (VRE) • Multidrug-resistant <i>Pseudomonas aeruginosa</i> • Drug-resistant nontyphoidal <i>Salmonella</i> • Drug-resistant <i>Salmonella</i> Typhimurium • Drug-resistant <i>Shigella</i> • Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) • Drug-resistant <i>Streptococcus pneumoniae</i> • Drug-resistant tuberculosis
<p>Concerning Threats</p> <ul style="list-style-type: none"> • Vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA) • Erythromycin-resistant Group A <i>Streptococcus</i> • Clindamycin-resistant Group B <i>Streptococcus</i>

Methicillin-Resistant *Staphylococcus Aureus*

MRSA was first identified five decades ago.⁷ Since then, MRSA infections have spread worldwide, appearing at a high incidence in several countries in Europe, the Americas, and the Asia-Pacific region.¹⁶ MRSA infections can be very serious and are among the most frequently occurring of all antibiotic-resistant threats.⁵ In the U.S., 11,285 deaths per year have been attributed to MRSA alone.¹²

MRSA is resistant to penicillin-like beta-lactam antibiotics.⁴ However, a number of drugs still retain activity against MRSA, including glycopeptides (e.g., vancomycin and teicoplanin), linezolid, tigecycline, daptomycin, and even some new beta-lactams, such as ceftaroline and ceftobiprole.¹⁶ However, MRSA has shown outstanding versatility at emerging and spreading in different epidemiological settings over time (in hospitals, the community, and, more recently, in animals).¹⁶ This compounds the epidemiology of MRSA infections and creates a challenge for infection-control systems that focus only on health care-associated infections (HAIs).¹⁶ Moreover, although resistance to anti-MRSA agents usually occurs through bacterial mutation, there have been reports of the transfer of resistance to linezolid and glycopeptide antibiotics, which is cause for major concern.¹⁶

Fortunately, the incidence of HAI MRSA infections seems to be declining, since aggressive preventive hygiene measures in hospitals in some areas (i.e., the Netherlands and United Kingdom) have had a positive effect.¹⁶ Between 2005 and 2011, overall rates of invasive MRSA dropped 31%; the largest declines (around 54%) were observed in

HAIs.⁵ This outcome provides evidence that infection control can be highly effective at limiting the spread of MRSA.¹⁶ However, during the past decade, rates of community-acquired MRSA infections have increased rapidly among the general population.⁵ While there is some evidence that these increases are slowing, they are not following the same downward trends that have been observed for hospital-acquired MRSA infections.⁵

Vancomycin-Resistant Enterococci

VRE presents a major therapeutic challenge.⁴ Enterococci cause a wide range of illnesses, mostly among patients in hospitals or other health care settings, including bloodstream, surgical-site, and urinary tract infections.^{4,5} VRE infections, often caused by *Enterococcus faecium* and less frequently by *Enterococcus faecalis*, have a lower prevalence and epidemiological impact than MRSA does worldwide, except for the U.S. and some European countries.¹⁶ An estimated 66,000 HAI Enterococci infections occur in the U.S. each year.⁵ The proportion of infections that are vancomycin-resistant depends on the species.⁵ Overall, 20,000 (30%) of hospital-acquired enterococcal infections per year are vancomycin-resistant, leading to 1,300 deaths.⁵

Few antimicrobial options are available to treat VRE.¹⁶ Antibiotics used against VRE include linezolid and Quinupristin /dalfopristin, while the role of daptomycin and tigecycline needs to be further defined.¹⁶ VRE remains a major threat; consequently there is tremendous interest in developing novel drugs that could have bactericidal activity against VRE, such as oritavancin.¹⁶

Drug-Resistant *Streptococcus pneumoniae*

S. pneumoniae can cause serious and sometimes life-threatening infections.⁵ It is a major cause of bacterial pneumonia and meningitis, as well as bloodstream, ear, and sinus infections.^{5,12} Resistant *S. pneumoniae* infections complicate medical treatment, resulting in nearly 1.2 million illnesses and 7,000 deaths per year.⁵ The majority of these cases and deaths occur among adults 50 years of age or older, with the highest rates among those 65 years of age or older.⁵ *S. pneumoniae* has developed resistance to drugs in the penicillin class and erythromycins, such as amoxicillin and azithromycin, respectively.⁵ It has also developed resistance to less commonly used drugs.⁵ In 30% of severe *S. pneumoniae* cases, the bacteria are fully resistant to one or more clinically relevant antibiotics.⁵

Fortunately, a new version of pneumococcal conjugate vaccine (PCV13), introduced in 2010, protects against infections caused by the most resistant pneumococcus strains, so rates of resistant *S. pneumoniae* infections are declining.⁵ From 2000 to 2009, an earlier pneumococcal conjugate vaccine, PCV7, provided protection against seven pneumococcal strains, but PCV13 expanded this protection to 13 strains.⁵ Use of this vaccine has not only prevented pneumococcal disease, it has also reduced antibiotic resistance by blocking the transmission of resistant *S. pneumoniae* strains.⁵

Drug-Resistant *Mycobacterium Tuberculosis*

Drug-resistant *M. tuberculosis* infections are a serious threat in the U.S., and an even more urgent threat worldwide.^{4,12} The WHO reported that in 2012, 170,000 people died from drug-resistant tuberculosis (TB) infections.^{4,12} *M. tuberculosis* is most commonly spread through the air.⁵ Infections caused by this bacterium can occur anywhere in the body but most often appear in the lungs.⁵ Of a total of 10,528 TB cases reported in the U.S. in 2011, antibiotic resistance was identified in 1,042, or 9.9%.⁵ The major factors driving TB drug resistance are incomplete, incorrect, or unavailable treatment and a lack of new drugs.⁵

In most instances, TB infections are treatable and curable with available first-line drugs, such as isoniazid or rifampicin; however, in some cases, *M. tuberculosis* can be

resistant to one or more of these first-line drugs.⁵ Treatment of drug-resistant TB can be complex, requiring longer treatment periods and more expensive drugs that often have more side effects.⁵ Extensively drug-resistant TB (XDR-TB) is resistant to most TB drugs, including isoniazid and rifampicin, any fluoroquinolones, and any of the three second-line injectable drugs (i.e., amikacin, kanamycin, and capreomycin); therefore, fewer treatment options are available for patients with XDR-TB, and the drugs that are available are much less effective.⁵ Although drug-resistant TB and XDR-TB infections are an increasing threat worldwide, these infections are uncommon in the U.S. because of the implementation of a robust TB infection prevention and management program.⁵

Carbapenem-Resistant Enterobacteriaceae (CRE)

Carbapenem-resistant Enterobacteriaceae (CRE) are a group of bacteria that have become resistant to “all or nearly all” available antibiotics, including carbapenems, which are typically reserved as the “treatment of last resort” against drug-resistant pathogens.^{4,5,12} An enzyme called New Delhi metallo-beta-lactamase (NDM-1) is present in some gram-negative Enterobacteriaceae bacteria (notably *Escherichia coli* and *K. pneumoniae*) that makes them resistant to virtually all beta-lactams, including carbapenems.⁴

Untreatable or difficult-to-treat infections due to CRE bacteria are on the rise among patients in medical facilities.⁵ An estimated 140,000 health care-associated Enterobacteriaceae infections occur in the U.S. each year; 9,300 of these are caused by CRE.⁵ Each year, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem-resistant *Klebsiella* species and carbapenem-resistant *E. coli*.⁵

MDR *Pseudomonas Aeruginosa*

P. aeruginosa is a common cause of HAIs, including pneumonia and bloodstream, urinary tract, and surgical-site infections.⁵ More than 6,000 (13%) of the 51,000 health care-associated *P. aeruginosa* infections that occur in the U.S. each year are MDR.¹⁶ Roughly 400 deaths per year are attributed to these infections.⁵ Some strains of MDR *P. aeruginosa* have been found to be resistant to nearly all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems.⁵

MDR *Acinetobacter*

Acinetobacter is a gram-negative bacterium that causes pneumonia or bloodstream infections, especially in critically ill patients on mechanical ventilation.⁵ Some *Acinetobacter* species have become resistant to all or nearly all antibiotics, including carbapenems, which are often considered to be the drug of last resort.⁵ About 12,000 health care-acquired *Acinetobacter* infections occur in the U.S. each year, and 7,300 (63%) of these are MDR (resistant to at least three different classes of antibiotics), causing 500 deaths per year.⁵

ESBL-Producing Enterobacteriaceae

Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae carry a broad-spectrum beta-lactamase enzyme that enables them to become resistant to a wide variety of penicillin and cephalosporin antibiotics.^{5,12} ESBL-producing Enterobacteriaceae cause 26,000 HAIs and 1,700 deaths per year.⁵ Some ESBL-producing Enterobacteriaceae are resistant to nearly all antibiotics in the penicillin and cephalosporin classes.⁵ In such cases, the remaining treatment option is an antibiotic from the carbapenem family.⁵ However, these drugs should be used with caution, since use contributes to resistance.⁵

Drug-resistant *Neisseria gonorrhoeae*

In recent years, drug-resistant forms of *N. gonorrhoeae*, the causative agent for the sexually transmitted disease gonorrhea, have begun to emerge in the U.S.¹ Gonorrhea is

characterized by discharge and inflammation of the urethra, cervix, pharynx, or rectum.⁵ While not normally fatal, gonorrhea spreads easily and can cause severe complications in reproductive functions.¹² The CDC estimates that more than 800,000 cases of gonorrhea occur annually, making it the second-most-frequently reported infectious disease in the U.S.⁵ Should drug-resistant *N. gonorrhoeae* become more widespread, it has been estimated that it would cause 75,000 additional cases of pelvic inflammatory disease, 15,000 cases of epididymitis, and 222 additional human immunodeficiency virus infections over a projected 10-year period.⁵

Cephalosporin-resistant *N. gonorrhoeae* is often resistant to other types of antibiotics, such as fluoroquinolones, tetracyclines, and penicillins.^{5,16} Infections caused by these bacteria will therefore likely fail empiric treatment regimens.⁵ In response to this challenge, the CDC has updated its treatment guidelines to recommend ceftriaxone, plus either azithromycin or doxycycline, as the first-line treatment for gonorrhea.¹²

THE CLINICAL AND ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE

Antibiotic-resistant infections are a substantial health and economic burden to the U.S. health care system, as well as to patients and their families.¹ They commonly occur in hospitals, due to the clustering of highly vulnerable patients, extensive use of invasive procedures, and high rates of antibiotic use in this setting.¹ Nearly two million Americans per year develop HAIs, resulting in 99,000 deaths, most due to antibacterial-resistant pathogens.¹ In 2006, two common HAIs (sepsis and pneumonia) were found to be responsible for the deaths of nearly 50,000 Americans and cost the U.S. health care system more than \$8 billion.¹

Antibiotic-resistant infections add considerable costs to the nation's already overburdened health care system. When first-line and then second-line antibiotic treatment options are limited or unavailable, health care professionals may be forced to use antibiotics that are more toxic to the patient and frequently more expensive.^{5,11} Even when effective treatments exist, data show that in most cases patients with resistant infections require significantly longer hospital stays, more doctors visits, and lengthier recuperations and experience a higher incidence of long-term disability.⁵ The duration of hospital stays for patients with antibiotic-resistant infections was found to be prolonged by 6.4 to 12.7 days, collectively adding an extra eight million hospital days.¹

Estimates regarding the medical cost per patient with an antibiotic-resistant infection range from \$18,588 to \$29,069.^{1,14} The total economic burden placed on the U.S. economy by antibiotic-resistant infections has been estimated to be as high as \$20 billion in health care costs and \$35 billion a year in lost productivity.¹ Antibiotic-resistant infections also burden families and communities due to lost wages and health care costs.^{1,15}

CONCLUSION

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics.¹⁴ This crisis is global, reflecting the worldwide

overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge.¹⁴ Antibiotic-resistant infections place a substantial health and economic burden on the U.S. health care system and population.¹ Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.^{2,7} Progress in these areas, as well as new agents to treat bacterial infections, will be discussed in Part 2 of this article.

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