The emergence of multidrug-resistant bacteria and the rapid global spread of carbapenem-resistant Enterobacteriaceae (CRE) have recently captured public attention, and some have asked whether the ongoing public health and scientific “war” against drug-resistant microbes, particularly bacteria, can ever be won. In fact, the challenge of antimicrobial resistance is an enduring threat that likely will never be eliminated. The threat is due, in part, to the inherent ability of microbes to replicate rapidly and mutate, offering them an evolutionary advantage in fending off hazards to their survival. Addressing the threat of antimicrobial resistance is a never-ending challenge.

The persistent nature of the struggle should come as no surprise. Although antimicrobial resistance has been inexorably linked to antibiotic use since the discovery of penicillin in 1928, resistance mutations occur even without the evolutionary pressure of antibiotics. In this regard, studies of bacteria in permafrost samples documented the existence of resistance genes 30,000 years ago. Thus, antibiotics did not create the problem of antimicrobial resistance in isolation; however, their use, and misuse, exacerbates it. Clinicians clearly play a role, when nearly three-quarters of adults presenting for care in the United States with acute bronchitis (generally of viral etiology) receive an unnecessary antibiotic. The agricultural sector also may contribute to the problem, as veterinary use represents about three-quarters of the antibiotic market in the United States. The majority of this use is for the promotion of animal growth, with subtherapeutic doses that can foster resistance. These problems are not unique to the United States, as countries in Europe and elsewhere have faced similar challenges in their agricultural and human health care sectors. In developing countries, the challenges are compounded by limited capacity for surveillance and poorly regulated sales.

These and other factors have combined to create a global crisis. In the United States alone, an estimated 23,000 deaths each year are associated with drug-resistant bacterial infections. The drug-resistant infections cost the US health care system an estimated $20 billion annually, with an additional estimated $35 billion in lost productivity. Methicillin-resistant Staphylococcus aureus is pervasive, found in approximately 50% of isolates in acute care hospitals in the United States. New strains of CRE rapidly spread in the United States from 1 to 44 states just in the last decade. More than half of bacterial isolates from urine samples from antenatal clinics in India showed resistance to commonly used antibiotics. This crisis is compounded by dwindling therapeutic options; although 16 antibiotics were approved by the US Food and Drug Administration between 1983 and 1987, only 2 were approved between 2008 and 2012.

A multifaceted, global solution to the problem of antimicrobial resistance is needed, one that combines effective prevention, appropriate use of therapeutics, passive surveillance and active case-finding, and a robust, multisector research enterprise for development of drugs and diagnostics, including market-based incentives for industry. Progress is being made; for example, the Centers for Disease Control and Prevention launched the Get Smart campaign to alter prescribing practices for common infectious complaints. The Institute for Healthcare Improvement has partnered with hospitals to improve protocols for preventing central line-associated bloodstream infections and ventilator-associated pneumonias, thereby obviating some need for broad-spectrum antibiotics. In addition, the industry has expanded the “pipeline” of new antibacterial drugs, with 14 agents currently in phase 3 clinical trials, spurred in part by innovation incentives such as the Generating Antibiotics Incentives Now Act, which provides extended market exclusivity for new drugs. The United States and the European Union both have instituted policies to decrease agricultural use of antibiotics.

The biomedical research enterprise at universities, academic medical centers, government laboratories, and other settings is a critical component of this multifaceted approach to addressing antimicrobial resistance, working collaboratively with the public health sector, industry, and clinical partners to provide the necessary tools. In this regard, the US National Institutes of Health recently refocused its efforts to address the scientific challenges posed by antimicrobial resistance. The approach is grounded in basic research in microbiology and related disciplines, yielding a more complete understanding of microbial pathogenesis. From these building blocks come the diagnostics, prevention methodologies, and treatments that serve the public good.

In noting the evolutionary advantage of microbes, Nobel Prize–winning bacterial geneticist Joshua Lederberg famously described the interaction between humans and microbes as a suspense thriller, “Our Wits Versus Their Genes.” The power of our wits—human intellectual and technical capacity—has greatly expanded with revolutions in genomic technologies that allow researchers to rapidly assemble vast amounts of data about microbes and their hosts, yielding targets for interventions. For example, investigators are mining the genomes of actinomycetes, natural producers of clinically relevant antibiotics. Preliminary studies indicate that 80% to 90% of the antibiotic compounds produced by actinomycetes have gone unrecognized. Based on this, researchers at the Broad Institute are sequencing 20 species of actinomycetes and studying gene products. This project, not feasible or even imaginable just one decade ago, could provide a treasure trove of data for antibiotic development.
In addition to the basic science that is integral to microbiology, scientists are actively translating pathogenesis research into tools for prevention, diagnosis, and treatment of infectious diseases. The importance of accurate diagnostics at point-of-care in efforts to thwart antimicrobial resistance cannot be overstated. Their use will bolster surveillance (including detection of outbreaks) and curb inappropriate antibiotic use through prompt identification of organisms and their antimicrobial sensitivities.

Among many advances, researchers recently showed that a new diagnostic tool can quickly distinguish between viral and bacterial etiologies of respiratory illness. The tool in this early-stage study is an intervention that could change clinical decision making, especially in urgent care settings, such as emergency departments and walk-in clinics. Moreover, the real-time polymerase chain reaction technology it uses could be applied to other testing scenarios, including identification of bacterial organisms and their resistance genes. Such tools are already in use for other diseases. For example, an automated test can identify the tuberculosis bacterium and resistance to rifampicin, a first-line tuberculosis drug, thus serving as a surrogate for the identification of multidrug-resistant tuberculosis. Basic and clinical research is also yielding novel approaches to therapeutics, from the development of new antibiotics to the repurposing of existing therapies. For example, compounds are being designed to directly target resistance mechanisms (eg, drugs that inhibit efflux pumps). An alternative approach inhibits the biofilm that bacteria use as a shield against the immune system.

Although improved diagnostics and therapeutics are essential tools in the fight against antimicrobial resistance, additional approaches must also be pursued. In this regard, vaccines are being developed to prevent infection with S. aureus, Neisseria gonorrhoeae, and other microbes for which treatment is complicated by the emergence of resistance. Moreover, the observation that bacteria live harmlessly in humans until a breach in host defenses develops has led investigators to consider the role of commensal bacteria and the microbiome in addressing resistance. Harnessing healthy bacteria to maintain defenses could combat future infection. In addition, basic pathogenesis studies have led investigators to target bacterial virulence factors, the mechanisms by which bacteria cause disease. Efforts to develop antitoxins, monoclonal antibodies against bacterial proteins, and secretion inhibitors are being pursued. Lastly, the use of natural predators against bacteria (such as bacteriophages, which destroy targets in a species-specific manner) would avoid the eradication of harmless commensals.

In summary, biomedical innovation combined with improved surveillance, prevention efforts, rapid diagnosis, market incentives to drive technology development, and curtailed misuse can meet the continual threat of antimicrobial resistance. Through this multisectoral approach, “our wits” will hopefully perpetually match “their genes.”

ARTICLE INFORMATION

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REFERENCES


