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Commentary

Antimicrobial Resistance Is a Global Health Emergency

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Leading experts have declared that the end of the age of antibiotics is imminent and that this development could undermine the foundation of much of modern medicine and public health.[1,2] Since antibiotics were first introduced into clinical practice some 80 years ago, microbes have been evolving ways to resist these drugs, but in recent years this problem of antimicrobial resistance (AMR) has been rapidly getting worse.[1]

It is estimated that there are at least 2 million cases per year of AMR infection in the United States directly resulting in at least 23,000 deaths.[2] In many nations around the world, the problem of AMR is worse than in the US. For example, rates of gram-negative resistance reach over 25% in parts of southern Europe, and all 6 regions of the World Health Organization (WHO) include countries that are reporting more than a 50% incidence of resistance of Klebsiella to third-generation cephalosporins.[3,4] There are no reliable estimates of the number of cases globally, largely because surveillance is incomplete; however, fragmentary evidence suggests that the problem is much worse in many developing countries.[1]

These infections occur in nearly all medical settings. A substantial percentage of childhood ear infections, urinary tract infections, community-acquired pneumonias, sexually transmitted infections, and wound and skin infections are caused by pathogens that have evolved resistance to one or more antibiotics to which they were previously sensitive. For example, all WHO regions report countries with rates of resistance to penicillin exceeding 50% in community-acquired pneumococcal infections, and half of the WHO regions have countries wherein the rate of gonorrhea resistance to third-generation cephalosporins exceeds 50%.[4]

An International Health Priority

The Global Health Security Agenda (GHSA) was launched by the US, partner nations, and international organizations in February 2014 as a 5-year plan to increase efforts globally to prevent, detect, and respond to infectious disease outbreaks. A key challenge identified by the GHSA is the emergence and spread of antimicrobial drug-resistant organisms.

Demonstrating the importance that the US government places on this issue, on September 18, 2014, the President's Council of Advisors on Science and Technology issued a report on Combating Antibiotic Resistance,[5] coinciding with a Presidential Executive Order[6] and a national strategy.[7] WHO, for its part, has spent most of 2014 developing a global action plan for tackling antimicrobial resistance that is to be delivered to the World Health Assembly in May 2015.[8]

Multidrug-Resistant Healthcare-Acquired Infections

Of the many clinical and public health challenges created by antimicrobial resistance, among the most serious are multidrug-resistant infections in hospitals and nursing homes. Multidrug-resistant (MDR) healthcare-associated infections (HAI) are no longer exceptional occurrences. For example, the CDC estimates that there are almost 7,000 cases per year

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of multidrug-resistant pseudomonas and 20,000 cases of vancomycin-resistant enterococcus (a third of all enterococcus healthcare-associated infections) in hospitalized patients in the US (excluding nursing home patients).[2]

What is most alarming, however, is the recent emergence of strains of pathogens resistant to nearly all (and in some rare cases, *all*) licensed antimicrobials.[1] This includes various strains of carbapenem-resistant enterobacteriaceae (CRE) that express the resistance enzymes, *Klebsiella pneumoniae* carbapenemase (KPC) or New Delhi Metallo-beta-lactamase-1 (NDM-1). These enzymes are encoded by genes that are carried on plasmids that are transferred from one bacterium to another without detriment to the hardiness of the bacteria. Several unrelated species of NDM-1–carrying bacteria have even been found in some drinking water samples in India.[9]

These strains of CRE can cause devastating infection with high fatality rates, typically in people who are debilitated, ill, or subjected to invasive medical procedures.[10] These infections result in an estimated 600 deaths per year in the US.[2] While this number is a small fraction of all AMR deaths (the most deaths are due to methicillin-resistant *Staphylococcus aureus* and drug-resistant pneumococcus), these nearly pan-resistant CRE infections were unheard of just a few years ago and are spreading. Healthy people can spread these bacteria along with their resistance genes, but they are typically unaffected by them; thus, as people travel, the resistance genes have been able to spread around the world. KPC was first discovered in 1996 in North Carolina; it is now found in most states of the US and many other countries from all continents.[11] In 2011, an outbreak of infections with KPC occurred at the National Institutes of Health Clinical Center that involved 18 patients over more than 6 months and resulted in 6 deaths.[12] NDM-1 was first discovered in Sweden in 2008 from a patient previously hospitalized in India and by 2010 was found on every continent.[1,13]

The Foundation of Modern Healthcare

The rapid rise of antimicrobial resistance not only makes treating life-threatening infections more difficult, it also jeopardizes the foundation of modern healthcare. Most routine surgical procedures, from appendectomies to joint replacements to coronary bypasses, rely on antibiotic prophylaxis to prevent life-threatening postoperative infections. If reliably effective antimicrobials are not available, these procedures will pose unacceptable risks. What morbidity and mortality risk is a reasonable person willing to accept for treatment of a non-life-threatening condition, such as a knee or hip replacement? Likewise, for potentially life-threatening conditions such as cancer, organ failure, or premature birth, at what rate of untreatable infection does the risk of the treatment (cancer chemotherapy, transplants, and neonatal care) exceed the risk of the disease? While it is difficult to determine how far in the future such a disturbing scenario lies, this fate is likely inevitable unless action is taken.

The Antimicrobial Pipeline

The evolution of antimicrobial resistance would not be as dire if there were a compensatory increase in new antimicrobial treatment options. In the past, as each broad spectrum antibiotic was rendered obsolete by resistance, a new one reliably appeared on the market. In the past 2 decades, there has been a well-described market failure in antimicrobial development, and the pipeline for new drugs has been thin for many years.[14] The number of new antimicrobials approved by the FDA decreased by 94% between the mid-1980s and 2010, with only 2 approved between the years 2008 and 2013.[14,15] In 2013, the Infectious Diseases Society of America (IDSA) identified only 7 new compounds targeting resistant gram-negative bacteria in its survey of the antibiotic landscape.[15]

The fundamental problem has been that the cost of developing and bringing a new antimicrobial to market may outweigh the expected return on investment, and as a result, investments have fallen. It is estimated that it costs on the order of $1 billion to bring a new drug to market.[16] For a drug such as a new antibiotic that should be used as sparingly as possible to delay development of resistance, the business case may be unconvincing. In the past few years, the US government's Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) and Biomedical Advanced Research and Development Authority (BARDA), both part of the Department of Health and Human Services, have had success in creating the public-private partnerships needed to move emergency countermeasures and some new antibiotics through the advanced development phase.

A Multipronged Strategy

Improving infection control practices, antibiotic stewardship, and surveillance are all critically important actions that should help to slow the rate of rise of resistance.[17] The CDC's 2013 Antibiotic Resistance Threats report and the President's executive order recognize the need for such a multipronged strategy.[2,6] Better surveillance of resistant strains will allow better antimicrobial selection by clinicians, and better stewardship practices will limit the unnecessary exposure of microbes to antimicrobials and help preserve our newest drugs for when they are truly needed. But even if these approaches were pursued with great effort, they can provide only a partial solution—the problem of AMR would not go away. Decades of experience has shown that healthcare-acquired infections cannot be completely eliminated, and as long as microbes can spread in healthcare settings, resistance will spread, too. Resistant microbes will continue to evolve as organisms are exposed to antimicrobials.

New and Innovative Therapies

One of the most important elements of a national and international strategy for AMR is the development of new therapeutics to help treat AMR infections. Discovering and developing new antibiotics will be important to help forestall some of the immediate consequences of widespread antimicrobial resistance. New research and development is needed, and novel approaches to address the market failure in antibiotics must be sought. But while the search for new broad-spectrum antimicrobials is a critical part of the near-term strategy to cope with this crisis, these products cannot, in and of themselves, win the arms race between pathogens and humans. Bacteria employ antimicrobials against each other and develop resistance to these molecules even without human intervention; consequently, AMR genes are found throughout the environment even without any exposure to man-made antibiotics.[18] Accordingly, each new antimicrobial that is discovered will at some point be followed by the emergence of resistance. Fundamentally new strategies to cope with infectious diseases need to be brought to bear alongside the antimicrobial strategies we are now pursuing.

Global Solutions for a Global Emergency

The problem of ARM is global and therefore the solutions should be as well. Only a concerted, multipronged, and sufficiently resourced international public-private effort can reverse the deepening crisis of antimicrobial resistance. To help promote awareness and stimulate innovative thinking, the editors of *Health Security* initiated this special feature on AMR to provide a venue for scholarly articles that inform national and international policy. The accompanying articles from both the US and Europe are examples of the diverse kinds of creative approaches that are needed to address this problem.

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