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Preserving the Lifesaving Power of Antimicrobial Agents

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AMONG THE MOST IMPORTANT MEDICINES EVER DISCOVERED, antimicrobial agents have saved millions of lives and improved the outcomes for countless patients since these drugs were introduced in the early 1930s. However, the effectiveness of these lifesaving resources is at risk. Many medical advances that physicians and patients take for granted—including cancer treatment, surgery, transplantation, and neonatal care—are endangered by increasing antibiotic resistance and a distressing decline in the antibiotic research and development pipeline.¹

Antibiotic-resistant infections have been estimated to cost the US health care system more than \$20 billion annually and result in more than 8 million additional days in the hospital.^{2,3} Drug resistance is both a public health and national security threat. Virtually all of the antibiotic-resistant pathogens that exist naturally today can be bioengineered through forced mutation or cloning, and existing pathogens could be genetically manipulated to make them resistant to currently available antibiotics. As underscored by recent reports of infections caused by strains of gram-negative bacteria producing the New Delhi metallo-beta-lactamase (NDM-1) enzyme, which confers multidrug resistance, antibiotic resistance is also a growing global public health threat.⁴

Addressing this complex problem is a high priority. Overcoming the impending public health crisis will require comprehensive, multipronged strategies to reduce the emergence of antimicrobial-resistant organisms and spur the development of new antibiotics.

Fixing the Broken Antibiotic Pipeline

The prospect of developing new antibiotics that offer meaningful benefits over existing drugs is currently bleak because the development pipeline is limited.¹ Most pharmaceutical companies have withdrawn from antibiotic research and development. This market failure has been driven by several forces. Because these essential drugs work so well and so fast—most are prescribed for only 7 to 14 days—they are simply not as profitable as drugs used to treat chronic conditions or lifestyle issues. Uncer-

tainties about requirements for regulatory approval and the major technical challenges inherent in identifying new classes of antibiotics present additional significant barriers to development. Once a successful new antibiotic clears these substantial hurdles and makes it to market, the profitability of the drug is further limited by effective antimicrobial stewardship programs and by the ability of microbes to rapidly adapt to antibiotics.

From 1983 to 1987, 16 new antibiotics were approved by the US Food and Drug Administration (FDA); from 2003 to 2007, just 5 were approved.⁵ Since 2008, only 2 have been approved (Brad Spellberg, MD, Harbor UCLA Medical Center, written communication, February 15, 2011). To raise awareness about the problem and the need for solutions, the Infectious Diseases Society of America (IDSA) launched the “Bad Bugs, No Drugs” advocacy campaign in 2004,¹ and more recently the 10 × ’20 Initiative, which calls for a global commitment to develop 10 new antibiotics by 2020.⁶

The initiative is an effort to mobilize key leaders and stakeholders around the specific aspirational goal of creating an antibiotic research and development effort powerful enough to produce 10 new, safe, and effective antibiotics with meaningful advantages over existing drugs within 10 years. More than 30 organizations have endorsed the initiative to date.

The ambitious 10 × ’20 goal could be reached if Congress would pass legislation that includes strong financial incentives for drug research and development, funding increases for research on resistance and drug and related diagnostics discovery, support for creation of public-private collaborations, and mandates for quick action by the FDA to provide regulatory clarity by publishing practical clinical trial guidance for industry. As part of FDA’s risk-benefit calculations, regulators need to consider the important clinical, public health, and national security benefits antibiotics provide as they develop guidance for design of clinical trials.

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Other Essential Strategies

It is estimated that as much as 50% of antibiotic use in human medicine is either unnecessary or inappropriate across all types of health care settings.⁷ The public and the broader health care community must be educated about when antibiotics are needed—and when they may do more harm than good—to help lower these rates and the resistance that results from inappropriate use. Indiscriminate antibiotic use can be dangerous, and aggressive control strategies can be effective, as the description of a 2008 linezolid-resistant *Staphylococcus aureus* outbreak in an intensive care unit in Spain illustrates.⁸

Effective antibiotic stewardship programs, combined with comprehensive infection prevention and control efforts, have been shown to limit the emergence and spread of antibiotic-resistant bacteria in health care facilities.⁷ These practices work, and they must be supported, expanded, and promoted in health care facilities of all sizes. Preserving the effectiveness of antibiotics is in everyone's interest and is everyone's responsibility.

Strengthening current surveillance, data collection, prevention and control, and research capabilities to better understand, track, and limit antimicrobial resistance is also essential. The Strategies to Address Antimicrobial Resistance (STAAR) Act,⁹ which more than 25 other organizations have endorsed, would improve federal coordination and funding in these areas. Many of the same groups have also endorsed the Preservation of Antibiotics for Medical Treatment Act, which would appropriately limit nonjudicious uses of antibiotics in animal agriculture.

Advancing the development of new, rapid point-of-care diagnostic tests also is a critical part of the solution because such tests could lead to better treatment decisions and reduce drug development costs by facilitating the conduct of clinical trials. Also needed are new antivirals because viruses also develop resistance, as highlighted by recent experience with seasonal and pandemic influenza.

A Call to Action

Health care professionals from across the medical and veterinary communities can play a critical role in addressing the resistance problem, from prescribing antimicrobial agents appropriately to raising awareness among political leaders and helping to put a human face on this public health threat.

There are signs of progress. International efforts including the establishment of a Transatlantic Task Force for Antimicrobial Resistance are under way. Antimicrobial resistance will be the theme for World Health Day in April 2011. The FDA and other federal agencies have publicly recog-

nized the urgent need for solutions to this problem. Bipartisan legislation has been introduced in Congress, including the Generating Antibiotic Incentives Now (GAIN) Act, which focuses on stimulating antibiotic and related diagnostic test development with incentives, such as extended exclusivity periods for certain antibiotics and diagnostic tests and priority regulatory review for applications for these types of products.

The stakes could not be higher. Without action, deaths and morbidity from antimicrobial resistance will continue to increase and the drug development pipeline will run dry. There is a moral obligation to patients and to the nation to prevent the unthinkable outcome of a return to the preantibiotic era and to ensure that these precious resources are available for future generations.

Published Online: February 22, 2011. doi:10.1001/jama.2011.279

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported that as president of the Infectious Diseases Society of America (IDSA) he receives a stipend. **Additional Contributions:** I thank the IDSA leaders who are committed to addressing this critical public health issue, including the members of the IDSA Antimicrobial Availability Task Force chaired by David N. Gilbert, MD, Providence Portland Medical Center and Oregon Health and Science University, Portland; the Antimicrobial Resistance Work Group chaired by Ruth Lynfield, MD, Minnesota Department of Health, St Paul; and the Research on Resistance Work Group chaired by Louis B. Rice, MD, The Warren Alpert Medical School of Brown University, Providence, Rhode Island; and John Heys of IDSA and Ashley Freeman of Emory University for assistance in preparing the manuscript, none of whom received compensation for their help.

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