Executive Summary: Global Antimicrobial Resistance Alerts and Implications

The Alliance for the Prudent Use of Antibiotics

The 2005 Global Advisory on Antibiotic Resistance Data (GAARD) Report, for the first time, provides a uniquely comprehensive view of drug resistance patterns across the major infectious diseases. It combines findings from diverse surveillance systems run by the world's leading infectious disease experts who are tracking resistance worldwide. The document focuses on the most troubling and urgent infectious disease threats whose cures are imperiled by antimicrobial resistance: HIV/AIDS, tuberculosis, malaria, gonorrhea, pneumonia, and hospital-associated infections.

By presenting this comprehensive view, the international scientists and clinicians who contributed to this report are sending an alert to policy makers and health professionals about the enormity of the threat posed by antimicrobial resistance, the need for surveillance to track resistance and guide treatment decisions, and the mandate for more appropriate use of antimicrobials. Prudent prescribing and dispensing of antimicrobials maximizes clinical therapeutic effectiveness while minimizing drug-related toxicity and containing health care expenses and drug resistance. Nationally, surveillance can promote evidence-based purchasing and distribution decisions and sound drug regulatory policies and quality control practices.

In 1998, the Alliance for the Prudent Use of Antibiotics (APUA) formed the GAARD project in an effort to support and learn from the existing surveillance infrastructure. GAARD brings together the world's largest surveillance systems, integrating antimicrobial resistance data from the various networks for special studies designed to inform public health policy.

Pharmaceutical companies agreed to contribute data from their ongoing surveillance systems as part of this unique public and private collaboration with the World Health Organization (WHO), the WHO Collaborating Centre on Antimicrobial Resistance, and the US Centers for Disease Control and Prevention (CDC). The combined group meets to analyze and interpret the relevance of the data at regular intervals.

Contributors to the 2005 GAARD Report include the GAARD group, as well as other prominent systems that are tracking resistance worldwide. In addition to unearthing important trends in drug resistance, the report illuminates not only the need for but also the paucity of coordinated local, national, and global surveillance data. There is a universal appeal for expanded surveillance of antimicrobial resistance globally, which will answer a public health "need to know."

THE GLOBAL BURDEN OF INFECTIOUS DISEASES

Although the toll of global infectious diseases is often depicted in graphs and statistics, it is fundamentally an epic tally of individual tragedies. A college football player in the United States contracts a community-acquired *Staphylococcus* infection in the locker room, and physicians frantically search a short list of antimicrobials that will cure this devastating new type of drug-resistant infection. A toddler in India dies of malaria or pneumonia, diseases that disproportionately strike infants and children. An elderly widower in the United States undergoes successful hip replacement surgery but dies of a *Staphylococcus* infection while recovering in the hospital. A woman in South Africa develops AIDS and dies prematurely, leaving 6 orphaned children, some of whom have been infected with HIV since birth. A husband and father in Kazakhstan dies of untreatable tuberculosis.

Respiratory infections. Pneumonia, an acute respiratory infection, remains the number 1 killer disease

Reprints or correspondence: Ms. Phakdey Chea, 75 Kneeland St., Boston, MA 02111 (phakdey.chea@tufts.edu).

Clinical Infectious Diseases 2005; 41:S221–3

1058-4838/2005/4104S4-0002$15.00

worldwide. In 1998, 3.5 million people, primarily children in the developing world, died of the infection [1]. In developing nations, *Haemophilus influenzae* type b causes pneumonia and meningitis, killing 450,000 children every year [2].

Malaria. More than 300 million cases of malaria are diagnosed each year; >1 million of these cases result in death. Most of those who die are children <5 years of age [2].

HIV/AIDS. An estimated 40 million persons worldwide are living with HIV/AIDS. About 20 million have died over the past 2 decades. Every day, 15,000 people become newly infected [2].

Gonorrhea. An estimated 60 million cases of gonorrhea occur annually [3]. The illness is linked to infertility in women and eye infections in newborns. Gonorrhea also amplifies the transmission of HIV/AIDS.

Tuberculosis. One-third of the world's population (~2 billion people) is currently infected with tuberculosis [1]; almost 9 million people have active disease. Of those with active disease, each individual can potentially transmit the disease to 10–15 others [4].

Staphylococcus *infection.* Hospital-associated infections are a serious problem. Of *Staphylococcus aureus* infections acquired in the hospital, 40%–60% are methicillin-resistant, and most are typically multidrug-resistant [5, 6]. The disease is a common complication of wounds, lower respiratory tract infections, septicemia, invasive devices, pressure sores, burns, and ulcers. First identified in hospitalized patients, infections due to methicillin-resistant *S. aureus* are beginning to strike healthy persons in the communities of affluent countries such as the United States.

THE SHADOW OF ANTIMICROBIAL RESISTANCE

The burden of disease is compounded by the emergence of resistance to antimicrobial drugs. With the discovery of antimicrobials in the 1940s, scientists prophesied the defeat of infectious diseases that had plagued humankind throughout history. Until recently, their claims were justified. Without these miracle drugs, modern medicine would come unhinged, and daily life would be an obstacle course of fear.

The bright prospect of antimicrobial therapy began to dim, however, when it soon became evident that disease-causing bacteria possess an amazing arsenal of strategies against medicine's "magic bullets." Unlike human beings, microorganisms have the ability to rapidly alter their genetic makeup and, in doing so, defy every antimicrobial on the market. Resistance to antimicrobial treatment was first recognized in bacteria. It is now known that viruses, such as those that cause HIV/AIDS, as well as parasites, such as those that cause malaria, can also resist drug treatment. The resistance that arises "when bugs meet drugs" has cast a shadow on the medical miracles we take for granted.

Antimicrobial resistance is undermining every clinical and public health program designed to contain infectious diseases worldwide. Limited access to medical care and effective treatments, the common practice of self-medicating, and the availability of counterfeit drugs have exacerbated drug resistance in the developing world. In affluent nations, infections acquired in settings such as hospitals and nursing homes are a major cause of illness and death. Each year in the United States alone, some 14,000 people die from resistant infections acquired in hospitals [1]. In addition, community-associated infections are emerging, both as independent epidemics and as primary sources of resistance in hospitals. If resistance to treatment continues to spread, our interconnected, high-technology world may find itself back in the dark ages of medicine before today's miracle drugs existed.

The problem of resistance has insinuated itself into virtually all of the infections that strike humankind. In this sense, it is a single overarching menace—a problem with common causes and common solutions, which can best be countered with integrated approaches to surveillance, prevention, and intervention. The need for global surveillance and more prudent antimicrobial use are underscored by the threat of bioterrorism. In the hands of the wrong person, genetically engineered and biologically repackaged pathogens can be made resistant to current antimicrobials and vaccines and could lead to widespread epidemics of infectious disease.

THE COSTS OF ANTIMICROBIAL RESISTANCE

In 1998, the total cost to US society of antimicrobial resistance was at least $4–$5 billion annually [7]. Fear of resistance leads physicians to prescribe alternative, potentially more costly drugs for initial treatment of infections. The extra costs for treatment of ear infections alone exceed $20 million annually in the United States [8]. In New York City, the extra annual cost for treating nearly 3000 patients infected with methicillin-resistant *S. aureus* ranged from $7 million to $10 million [9]. Medication to treat 1 person for tuberculosis resistant to several drugs can cost as much as 100 times more than traditional treatment for susceptible strains (US $20 vs. US $2000) [1].

Despite the 20th century's advances, dangerous new trends in the new millennium threaten our ability to outpace antimicrobial resistance. Across the entire array of global infectious diseases, the shadow of antimicrobial resistance is lengthening.

Resistance arises to multiple drugs. Antimicrobial resistance often involves resistance to one specific "first-line" antimicrobial. First-line drugs are the treatments developed decades ago that have traditionally been used to fight infection. Increasingly, however, as bacteria wage war on these mainstays of therapy, resistance to >1 class of drugs develops, and "op-

timal-choice" antimicrobials become obsolete. This phenomenon, called multidrug resistance, requires more complex treatment regimens involving "second-line" and even "third-line" antimicrobials. Often these costly alternative drugs are affordable only in industrialized nations. In effect, antimicrobial resistance catapults developing nations backward to a time when no treatments existed at all.

Development of new drugs is declining. At the same time that existing treatments are becoming undermined by drug resistance, new treatment solutions seem ever more distant. Economic disincentives drive pharmaceutical companies away from antimicrobial research and development and toward more profitable drugs that treat chronic illnesses, such as diabetes, arthritis, and heart disease, or lifestyle concerns, such as impotence. The profit-driven emphasis on chronic diseases threatens development of new drugs as well as the future of surveillance systems developed to monitor antimicrobial resistance in deadly infectious pathogens.

SURVEILLANCE: KEY TO TRACKING AND TAMING RESISTANCE

Surveillance networks throughout the world have improved our ability to detect, monitor, and manage antimicrobial resistance. Information from coordinated surveillance studies tells us how antimicrobial resistance varies geographically and over time. Constant monitoring of rates of resistance throughout the world can help target resources efficiently. This rational targeting of resources, in turn, cuts the cost of health care by preserving the power of current first-line antimicrobials. Investigating why some locales have low rates of resistance, whereas others have high rates, also offers clues to the underlying causes of drug resistance. The development and expansion of laboratory systems responsible for collection of surveillance data are essential components of our mission to monitor antimicrobial resistance. These facilities not only assist physicians in the proper diagnosis and treatment of infections but also help disseminate treatment guidelines and strategies.

If the 2005 GAARD Report has one overriding message, it is that no nation and no single surveillance system can stand alone in heading off antimicrobial resistance. As economic globalization has proven, all of our lives are interconnected. Infectious disease pathogens—including drug-resistant organisms—need no visas. They can cross borders with ease and quickly transform a local outbreak into a global scourge. In this sense, the division between the "industrialized" and "developing" worlds has disappeared.

Acknowledgments

The Alliance for the Prudent Use of Antibiotics (APUA) thanks the following for their expertise and generous commitment of time and their dedication to the process and goals of the Global Advisory on Antibiotic Resistance Data (GAARD) Project: Mohamed Abdel Aziz, Douglas J. Biedenbach, Thomas R. Fritsche, David H. Howard, Khalid H. Ibrahim, Ronald N. Jones, Laura M. Koeth, Donald E. Low, Linda A. Miller, Piero L. Olliaro, Lucia Palmisano, Robert P. Rennie, Helio S. Sader, R. Douglas Scott II, J. W. Tapsall, Mark A. Toleman, Philip J. Turner, Stefano Vella, Timothy R. Walsh, J. Todd Weber, and Abigail Wright. The following APUA staff members dedicated time and effort to the completion of this project: Elizabeth Andrews, Phakdey Chea, Carol Cogliani, Stuart B. Levy, Bonnie Marshall, Thomas F. O'Brien, John Stelling, and Kathleen T. Young.

Financial support. GlaxoSmithKline Research and Development; Aetna, Incorporated; the Chiron Foundation; and the National Institutes of Health (grant 5U24AI050139-03).

Potential conflicts of interest. No conflicts.

References

1. World Health Organization (WHO). Overcoming antimicrobial resistance, World Health Organization report on infectious diseases. Geneva: WHO, **2000**.
2. World Health Organization (WHO). State of the world's vaccine and immunizations. Geneva: WHO, **2002**.
3. World Health Organization (WHO). Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific region: update on the gonococcal antimicrobial surveillance program (GASP), 1992 to 1998. STI/HIV/AIDS surveillance report, vol. 14. Geneva: WHO, **1999**: 32–7.
4. World Health Organization. Tuberculosis: infection and transmission. **2005**. Available at: http://www.who.int/mediacentre/factsheets/fs104/en/. Accessed 29 September 2004.
5. Weinstein RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerg Infect Dis **2001**; 7:188–92.
6. European Antimicrobial Resistance Surveillance System (EARSS). EARSS annual report 2002. Bilthoven, The Netherlands: EARSS Management Team, members of the Advisory Board, and national representatives of EARSS, **2003**. Available at: http://www.earss.rivm.nl/PAGINA/DOC/rep2002/annual-report-2002.pdf. Accessed 29 September 2004.
7. Institute of Medicine. Microbial threats to health: emergence, detection, and response. Washington, DC: National Academies Press, **1998**.
8. Howard DH. Resistance-induced antibiotic substitution. Health Econ **2004**; 13:585–95.
9. Infectious Diseases Society of America (IDSA). Bad bugs, no drugs: as antibiotic discovery stagnates… a public health crisis brews. Alexandria, VA: IDSA, **2004**.