

# **Shadow Epidemic**

**The Growing Menace of Drug Resistance**

**2005 GAARD  
Report**

## Acknowledgments

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*Many of the select findings included in this document are the contribution of  
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## Objectives and Significance

*Shadow Epidemic*—the 2005 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 tracking resistance around the world. 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-acquired infections.

By presenting this comprehensive view, the international scientists and clinicians who contributed to this report are sending an alert to policy makers and medical professionals about the enormity of the antimicrobial resistance threat, the need for surveillance to track resistance and guide treatment decisions, and the mandate for more appropriate antimicrobial use. Prudent antimicrobial prescribing and dispensing 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 Global Advisory on Antibiotic Resistance Data (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 on-going surveillance systems as part of this unique public and private collaboration with the World Health Organization (WHO), the World Health Organization Collaborating Centre on Antimicrobial Resistance, and the United States

### **Current GAARD Steering Committee Members**

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The World Health Organization's Collaborating Centre for Surveillance of Antimicrobial Resistance

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Centers for Disease Control and Prevention (CDC). The combined group meets to analyze and interpret the relevance of the data at regular intervals.

The 2005 GAARD Report contributors include the GAARD group as well as the other prominent systems tracking resistance worldwide. In addition to unearthing important trends in drug resistance, the report not only illuminates the need, but the paucity of coordinated local, national, and global surveillance data.

## Executive Summary

This Executive Summary highlights the findings of the 2005 GAARD Report—a larger report is planned for release early next year in *Clinical Infectious Diseases*. A snapshot of these findings is made available now because scientists have identified mounting new trends in antimicrobial resistance that beg the immediate attention of public health policy makers and medical professionals. There is a universal appeal for expanded surveillance of antimicrobial resistance globally, which will answer a public health “need to know.”

### **Need to Know**

#### **Locally, Nationally and Globally**

Frequency of antimicrobial resistance

Type of antimicrobial resistance

Trends of resistance over time

Availability and use of antimicrobial drugs

## The Global Burden of Infectious Diseases

While 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 staph infection in the locker room and physicians frantically search a short list of antibiotics 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 staph infection while recovering in the hospital.

- A woman in South Africa develops AIDS and dies prematurely leaving six orphaned children, some of whom have themselves been infected with the virus since birth.
- A husband and father in Kazakhstan dies of untreatable tuberculosis.

**Respiratory Infections** Pneumonia, an acute respiratory infection remains the number one disease killer worldwide. In 1998, 3.5 million people, primarily children in the developing world, died of the infection.<sup>1</sup> In developing nations, *Haemophilus influenzae* type b (Hib) causes pneumonia and meningitis, killing 450,000 children every year.<sup>2</sup>

**Malaria** More than 300 million cases of malaria are diagnosed each year; more than a million of these cases result in death. Most of those who succumb are children under the age of five.<sup>2</sup>

**HIV/AIDS** An estimated 40 million persons worldwide are living with HIV/AIDS. Approximately 20 million have died over the past two decades. Every day, 15,000 people become newly infected.<sup>2</sup>

**Gonorrhea** An estimated 60 million cases of gonorrhea occur annually.<sup>3</sup> 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 (about two billion people) is currently infected with tuberculosis;<sup>1</sup> close to nine million victims have active disease. Of the latter, each can potentially transmit the disease to 10 to 15 other individuals.<sup>4</sup>

**Staphylococcus Infection** Hospital-acquired infections are a serious problem. Forty to sixty percent of all *Staphylococcus aureus* acquired in the hospital are methicillin-resistant (MRSA) and typically multi-drug resistant.<sup>5,6</sup> 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, MRSA infections are beginning to strike healthy individuals in the community in 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. And 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 arse-

nal of strategies against medicine's "magic bullets." Unlike human beings, microorganisms have the ability to rapidly alter their genetic make-up—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-medication, 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.<sup>1</sup> In addition, community-acquired 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-tech world may find itself back in the dark ages of medicine, before today's miracle drugs ever existed.

The problem of resistance has insinuated itself into virtually all 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 coordinated global surveillance and the need for 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 infectious disease epidemics.

### The Costs of Antimicrobial Resistance

- In 1998 the total cost to US society of antimicrobial resistance was at least \$4 to \$5 billion annually.<sup>7</sup>
- Fear of resistance leads physicians to prescribe alternate, potentially more costly drugs for initial treatment of infections. The extra costs for treatment of ear infections alone exceed \$20 million annually in the U.S.<sup>8</sup>
- In one city (New York City), the extra annual cost for treating nearly 3,000 MRSA-infected patients ranged from \$7 to \$10 million.<sup>9</sup>
- Medication to treat one person for tuberculosis resistant to several drugs can cost as much as 100 times more than traditional treatment for

susceptible strains (USD \$20 versus USD \$2,000).<sup>1</sup>

In spite of the twentieth 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 more than one class of drugs develops, and “optimal-choice” antimicrobials become obsolete. This phenomenon, called multi-drug resistance (MDR), 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.



### New Drug Development is Declining

At the same time as existing treatments are becoming undermined by drug resistance, new solutions seem ever more distant. Economic disincentives drive pharmaceutical companies away from antimicrobial R&D 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 new drug development 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 resistance rates throughout the world can help target resources efficiently. This rational

Studies included in the **GAARD Report** reveal that the shadow of antimicrobial resistance has fallen on the world's most serious public health threats:

- Malaria is worsening to a large extent because of the emergence and spread of parasites resistant to drug treatment. Continued use of failing drugs and inadequate treatment contribute to the growth of treatment resistance and to increased malaria morbidity and mortality.
- Community-acquired MRSA (CA-MRSA), which bears significant similarities to and differences from HA-MRSA (hospital-acquired), appears to be on the rise and has been described in several well-defined populations, such as children, incarcerated persons, Alaska Natives, Native Americans, Pacific Islanders, sports participants, and military personnel.
- Some HIV strains are resistant to one or more classes of antiviral drugs.
- The Western Pacific Region has seen a dramatic rise in quinolone-resistant strains of gonorrhea (exceeding 50%)—rendering quinolone therapy totally ineffective in some areas. Reduced susceptibility and treatment failures have also been observed with the newest cephalosporin agents.
- High concentrations of MDR-TB are found in Eastern Europe and in countries of the former Soviet Union.
- Resistance to the latest generation of penicillins and cephalosporins from beta-lactamases\* is rapidly increasing.

\*Beta-lactamase: an enzyme produced by some bacteria that degrades penicillins and cephalosporins.

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 resistance rates while others have high rates also offers clues to the underlying cause of drug resistance. The development and expansion of laboratory systems responsible for surveillance data collection 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” world has disappeared.



### Select Findings

The 2005 GAARD Report reveals a common story of increasing treatment failures often attributable to misuse of these powerful therapeutic agents and the lack of knowledge about local resistance threats. This summary presents highlights of a larger report, planned for release in *Clinical Infectious Diseases* in 2005. The findings are being presented as an early release “wake up” call. Antimicrobial resistance should be viewed with the recognition that physicians ideally expect 100% effectiveness, 0% resistance when treating a deadly infection. While our initial wonder drugs did hold that promise, today we have an age of multi-drug resistance and increasing treatment failures.

### **Pneumonia**

“Antimicrobial Resistance in *Streptococcus pneumoniae*” (Donald E. Low)

- *S. pneumoniae*, the bacterium responsible for most cases of pneumonia, is increasingly resistant to traditional penicillin therapy and to newer macrolide antimicrobials.
- Global penicillin resistance rates for *S. pneumoniae* range from 5.8% (Canada) to as high as 54% (Hong Kong).
- Macrolide resistance now exceeds penicillin resistance in some regions. Resistance rates for *S. pneumoniae* range from 11.1% (Canada) to approximately 72% (Hong Kong and Japan).
- Global fluoroquinolone resistance rates for *S. pneumoniae* are comparatively low (1% to 18%), but are rising at an alarming rate worldwide.

“Antimicrobial Resistance in *Haemophilus influenzae*. How Can We Prevent the Inevitable?” (Khalid H. Ibrahim)

*H. influenzae* is a major cause of respiratory tract infections and meningitis, especially in the elderly and children. A vaccine is available, but only for certain strains of this species.

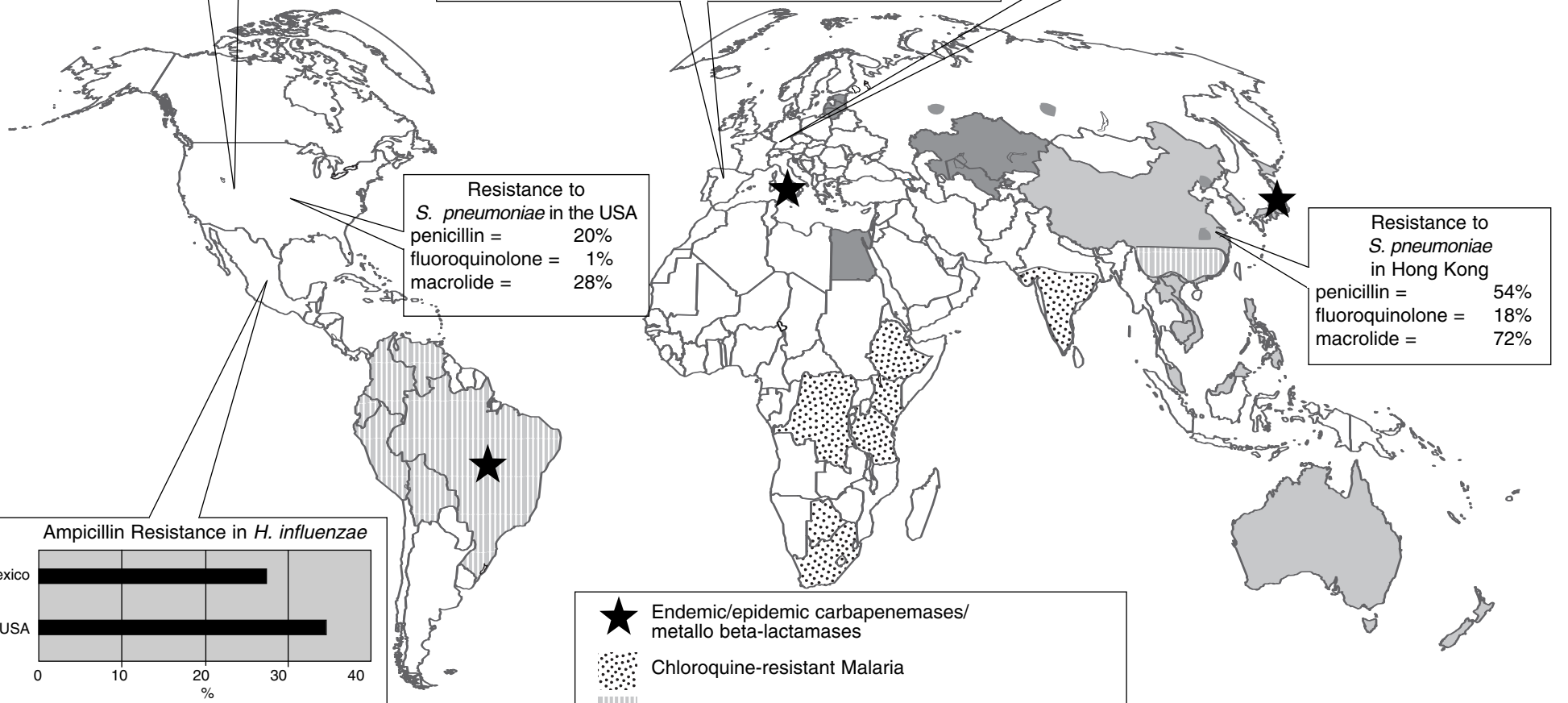
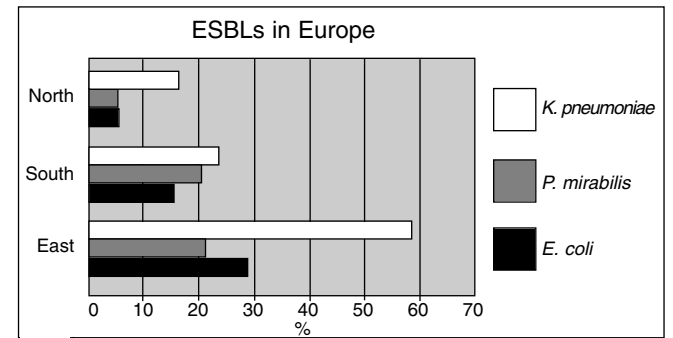
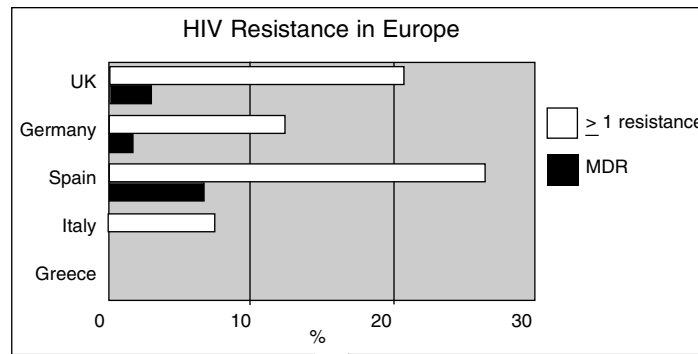
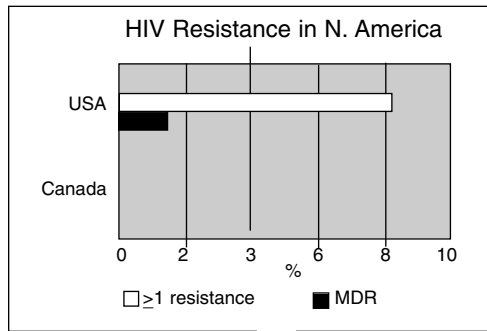
- *H. influenzae* resistance to ampicillin ranges from 6% to 43% depending on the geographic source.
- The patterns of antimicrobial resistance for *H. influenzae* are not well understood. Recent evidence suggests that *H. influenzae* resistance patterns in the community may mimic those found in *S. pneumoniae*. The potential for emergence of resistance to macrolide and fluoroquinolone classes is cause for concern.

### **HIV/AIDS**

“The Global Status of Resistance to Antiretroviral Drugs” (Stefano Vella and Lucia Palmisano)

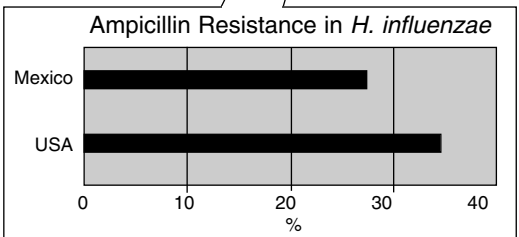
- The introduction of highly active antiretroviral therapy—HAART—has changed the face of HIV/AIDS in resource-rich countries by dramatically reducing mortality and morbidity. These advances have only minimally translated to the developing world, where the impact of the epidemic is catastrophic.
- The success of HAART is increasingly threatened by HIV resistance to antiviral drugs, which will likely continue to emerge and spread. Paradoxically, the increased access to HAART is likely to increase the size of epidemics.
- At present, there are no reliable estimates of the burden of HIV resistance at the global level, although a number of national and regional surveillance projects have been launched.
- Among the most representative datasets, the CATCH (Combined Analysis of Resistance Transmission over Time of Chronically and Acutely Infected HIV Patients in Europe) study has measured resistance in 17 European countries (1996-2002) and found a frequency of 9.6% resistance to any drug class, and upwards of 1.7% to two or more drug classes.

# Tracking Antimicrobial Resistance: Selected Problems around the Globe\*



Resistance to *S. pneumoniae* in the USA  
 penicillin = 20%  
 fluoroquinolone = 1%  
 macrolide = 28%

Resistance to *S. pneumoniae* in Hong Kong  
 penicillin = 54%  
 fluoroquinolone = 18%  
 macrolide = 72%



- ★ Endemic/epidemic carbapenemases/metallo beta-lactamases
- Chloroquine-resistant Malaria
- ▨ Multiresistant malaria
- MDR-TB concentrated area (>10%)
- Quinolone-resistant *N. gonorrhoeae* (>5%)
- \*Absence of any data may reflect low or no resistance or lack of surveillance data

\*Data provided by the surveillance systems are acknowledged in this report in Appendix V.

**Malaria**

“Drug Resistance Hampers Our Capacity to Roll Back Malaria” (Piero Olliario)

- Malaria is worsening to a large extent because of the emergence and spread of parasites resistant to drug treatment. Continued use of failing drugs and inadequate treatment contribute to the rise in treatment resistance and to increased malaria morbidity and mortality.
- Pharmacological, operational and epidemiological factors contribute to the emergence and spread of parasite resistance. Resistance occurs as a result of spontaneously occurring mutations or gene amplification and appears to establish itself more readily in areas of low transmission and intense drug use.
- The extent of the problem owes mostly to the very limited armory of drugs currently available to treat malaria, which is the result of neglect of the development of drugs to fight the disease.
- It is vital that newer drugs with novel chemical structures and modes of action are discovered and developed, and that drugs are protected against resistance through combination therapies.

**Tuberculosis**

“Global Epidemiology of Anti-TB Drug Resistance” (Mohamed Abdel Aziz)

Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, two traditional first-line antimicrobials.

- MDR-TB has reached alarming and unprecedented levels in every corner of the globe. High concentrations of MDR-TB are found in East Europe and in countries of the former Soviet Union (Kazakhstan, the Aral Sea regions of Uzbekistan and Turkmenistan, Estonia, Latvia, Lithuania and some Oblasts in the Russian Federation). Ecuador and certain provinces of China are also experiencing high MDR-TB levels.
- Treatment of MDR-TB is much more complex, prolonged and significantly more expensive than treatment for drug-susceptible cases. Mortality is high as well.
- Control of tuberculosis is undermined by the HIV epidemic.
- The limited surveillance of high-burden nations such as China and India is worrisome, as it is suspected that the rate of MDR-TB is high in these areas.
- The strengthening of laboratory networks in conjunction with improved surveillance is essential to TB control.

**Gonorrhea**

“Antimicrobial Resistance in *Neisseria gonorrhoeae*” (J.W. Tapsall)

- Current data from regional and country-based surveillance systems reveal that traditional antimicrobials such as penicillins and tetracyclines, as well as newer quinolone antimicrobials, are increasingly ineffective in treating gonorrhea. The usefulness of newer macrolides and spectinomycin is also limited.
- The Western Pacific Region has seen a dramatic rise in quinolone-resistant strains of gonorrhea (exceeding 50%)—rendering quinolone therapy totally ineffective in some areas. Reduced susceptibility and treatment failures have also been observed with the newest cephalosporin agents.
- The remaining effective therapies are often too costly for afflicted populations.
- Antimicrobial resistance has slowed the prospects for control of gonorrhea.
- Multi-drug-resistant gonorrhea from endemic Asian sources is spreading to the Western hemisphere.
- Gonorrhea is now recognized as a significant amplifier of HIV transmission. Transmission of HIV in those with gonorrhea may be as much as five times that for those without gonorrhea. Persons with gonorrhea are also more susceptible to acquisition of HIV infection.

**Methicillin-Resistant *Staphylococcus* Infections**

“Community-acquired *Staphylococcus aureus*” (J. Todd Weber)

Historically, multi-drug-resistant staph infections (methicillin-resistant *Staphylococcus aureus*, or MRSA) are acquired by persons in hospitals, nursing homes and other healthcare institutions. These infections are known as healthcare-acquired MRSA (HA-MRSA).

- Community-acquired MRSA (CA-MRSA), which bears significant similarities to and differences from HA-MRSA, appears to be on the rise and has been described in several well-defined populations, such as children, incarcerated persons, Alaska Natives, Native Americans, Pacific Islanders, sports participants, and military personnel.
- Proven, generalizable strategies and programs for preventing the emergence and spread of CA-MRSA are lacking.
- Further surveillance, epidemiological and clinical studies on CA-MRSA infections are necessary for documenting the extent of the problem and for developing and evaluating effective prevention and control efforts.

### **Mechanisms of Antimicrobial Resistance**

#### **“Extended-spectrum beta-lactamases” (Philip J. Turner)**

- Antimicrobial resistance due to ESBL (extended spectrum beta-lactamase) production is rapidly increasing. According to MYSTIC data, 11% - 30% of strains tested (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*) may be ESBL-producers.
- ESBLs are mechanisms bacteria use to thwart the treatment of such hospital-acquired diseases as pneumonia, septicemia, and intra-abdominal sepsis; they are also occurring increasingly in community-acquired urinary tract infections. Antimicrobials such as the cephalosporins, which have been historically used to treat these diseases, are losing their power, often leaving only limited treatment options as alternative choices.
- To ensure effective treatment, laboratories should routinely test for the presence of ESBLs.

#### **“Metallo-beta-Lactamases” (Ronald N. Jones, Douglas J. Biedenbach, Helio S. Sader, Thomas R. Fritsche, Mark A. Toleman and Timothy R. Walsh)**

Carbapenems are last-line antimicrobial agents. The increase in production by bacteria of metallo-beta-lactamases, which destroy carbapenems, is particularly worrisome.

- New types of metallo-beta-lactamases are becoming dominant causes of resistance in gram-negative bacilli in Asia, Europe and Latin America. The first metallo enzymes were also detected in the U.S. in late 2002.
- Metallo-beta-lactamases are usually harbored by species with intrinsic resistances, so that the enzyme genes can carry resistances to other antimicrobial classes, producing various multi-drug-resistant strains for which there are no therapeutic options.

### **Impact of Surveillance Efforts**

#### **“Evolving Concepts of Pharmaceutical Company Sponsored Surveillance Studies” (Linda A. Miller and Laura M. Koeth)**

- Large, multi-year studies like the Alexander Project are instrumental in tracing the evolution of antimicrobial resistance.
- Data from these studies can be utilized in mathematical models, which are helpful in trying to predict future patterns of antimicrobial resistance.
- High quality data are crucial to useful surveillance. There has been an overall decrease in the number of antimicrobial resistance studies conducted by pharmaceutical companies. Though these companies

continue to support surveillance, the scale and scope of such studies will likely be downsized, reflecting the companies' preferential interest in chronic disease treatments and lifestyle drugs.

- Research efforts should focus on geographic areas with low resistance rates as well as those with high resistance rates. To date, little research has focused on areas with low resistance rates, from which much could be learned.

### **Cost of Resistance**

#### **“Economic Burden of Drug Resistance” (David H. Howard and R. Douglas Scott III)**

The economic burden of antimicrobial resistance is believed to be enormous, but few studies have successfully evaluated these costs.

- Estimates of the economic impact of antimicrobial resistance should include direct costs, such as the cost of having to use more expensive drugs to replace less expensive traditional drugs. In addition, estimates should include costs of illness and disability associated with antimicrobial resistance, as well as the economic implications of deaths caused by the inability to cure formerly treatable infectious diseases.
- Although studies that yield more specific information are needed, a few reports have quantified certain aspects of the economic burden:
  - Costs for hospitalized patients infected with resistant bacteria are over \$20,000 (USD per patient) higher than costs for patients infected with susceptible strains.
  - Fear of resistance leads physicians to prescribe alternate, more costly drugs for the initial treatment of infections. The extra costs for treatment of ear infections alone exceed \$20 million (USD) annually.
  - As resistance levels increase, hospitals and other providers will need to spend large sums to limit the spread of resistant bacteria. Simply requiring staff and visitors in an intensive care unit to wear gowns and gloves increased costs by over \$70,000 (USD) annually in a single intensive care unit.

## Selected Conclusions and Recommendations from the Full Report

### Need to Know

Antimicrobial resistance is a global pandemic that shadows every patient who contracts any infectious disease. It is, in effect, an independent disease entity, complicating therapies and claiming lives around the world. Burgeoning drug resistance also casts a shadow on increasingly strained health care budgets by dramatically raising the costs of treatment and infection control.

Among the most serious consequences:

- Multi-resistant gram-negative bacilli are becoming untreatable, particularly with the mounting emergence of metallo-beta-lactamases.
- Community-acquired MRSA is now on the rise, emerging among athletes, military personnel, prisoners and children.
- Cases of drug-resistant HIV/AIDS are increasing.
- Chloroquine-resistant malaria is spreading through the developing world. While alternative drugs are available, they are not affordable in countries malaria most affects.

Without public attention and urgent action, drug resistance threatens to catapult the world back to a pre-antimicrobial era. To date, governments and industry have paid little heed to continual calls for change. This report is a plea from the world's leading experts who track the spread of resistance: We must wake up to the danger before it is too late. Fuller lists of recommendations appear in the WHO Global Strategy and will be published in the full 2005 GAARD Report, forthcoming in *Clinical Infectious Diseases*.

While this summary cannot discuss all necessary action, what is clear is that a large and dedicated investment is needed worldwide to chart and contain antimicrobial-resistant organisms and preserve our ability to treat infectious diseases. Coordinated programs to 1) improve knowledge of the frequency of resistance, 2) promote appropriate use of existing antimicrobials, and 3) discover new drugs, diagnostics and infection control approaches, will yield high payoff.

Deadly drug-resistance is not only on the horizon—it is in our midst. We are calling for nothing less than large-scale, coordinated, public-private action involving industry, professional societies and public health groups. After 25 years of calls for action, what is needed most is immediate leadership and substantial investments from governments around the world.

The findings in this report demonstrate the shadow of drug resistance is lengthening across the globe. To forestall a total eclipse of effective infectious

disease treatment, organizations and governments must provide a dramatic increase of funding for groups tracking and controlling drug resistance. These include CDC, FDA (Food and Drug Administration), NIAID (National Institute of Allergy and Infectious Diseases, National Institutes of Health), WHO, USAID (United States Agency for International Development), USDA (United States Department of Agriculture) and public/private partnerships.

### Major Surveillance and Control Recommendations

- Support national and international surveillance efforts to determine the frequency of resistance to antimicrobials.
- Research and develop new therapeutic agents with novel modes of action to treat and control resistant infections.
- Establish infectious disease protocols to promote prudent antimicrobial prescribing and dispensing practices to improve quality of care.
- Improve access to, and use of high-quality diagnostic, infection control, and treatment services.

## Contributing Surveillance Networks

### The Global Advisory on Antibiotic Resistance Data (GAARD)

The GAARD project was established in 1998 as a public-private collaboration. GAARD brings together the world's largest surveillance systems, using integrated antimicrobial resistance information from the various systems for focused studies. It operates under the following four objectives: 1) to serve as a comprehensive data source on antimicrobial resistance and global surveillance; 2) to communicate clinically and scientifically important information on antimicrobial resistance to clinicians, public health practitioners, scientists and policy makers; 3) to facilitate development of national surveillance systems by supporting capacity-building efforts in developing countries and by linking local surveillance systems with larger networks; and 4) to conduct and encourage research on resistance using collected data and isolates.

Data from the surveillance networks indicated on the following page are included in *Shadow Epidemic*. Their respective organisms and geographic areas of study are also listed.

Surveillance network	Organisms covered	Geographic coverage
Active Bacterial Core Surveillance (ABCs)—U.S. Centers for Disease Prevention and Control	<i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , Group A <i>Streptococcus</i> , Group B <i>Streptococcus pneumoniae</i>	U.S.A.
Alexander Project—GlaxoSmithKline	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Streptococcus pyogenes</i>	North and South America, Asia-Pacific, Africa, Middle-East and Europe
Australian Gonococcal Surveillance Programme (AGSP)	<i>Neisseria gonorrhoeae</i>	Australia
Canadian Bacterial Surveillance Network (CBSN)	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	Canada
Gonococcal Antimicrobial Surveillance Programme (GASP)	<i>Neisseria gonorrhoeae</i>	Australia and Asia-Pacific
Gonococcal Isolate Surveillance Project (GISP)	<i>Neisseria gonorrhoeae</i>	U.S.A.
Gonococcal Resistance to Antimicrobials Programme (GRASP)	<i>Neisseria gonorrhoeae</i>	U.K.
Global HIV Drug Resistance Surveillance Network (HIVResNet)	HIV	Worldwide
Meropenem Yearly Susceptibility Test Information Collection Surveillance Study (MYSTIC)—AstraZeneca	Many gram-positive and gram-negative bacterial species	Europe, South America, North and Central America and Asia-Pacific
National Health and Nutrition Examination Survey (NHANES)	<i>Staphylococcus aureus</i>	U.S.A.
SENTRY Antimicrobial Surveillance Program—Bristol-Myers Squibb	Many gram-positive and gram-negative bacterial species	Europe, South America, North and Central America, Asia-Pacific and South Africa
TARGETed Surveillance—LIBRA, Bayer HealthCare AG	UTI and RTI pathogens	North America, Europe and Africa
Tracking Resistance in the United States Today (TRUST)—Ortho-McNeil	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>	U.S.A.
WHO/IUATLD—Global Project on Anti-Tuberculosis Drug Resistance Surveillance	<i>Mycobacterium tuberculosis</i>	Europe, South America, North and Central America, Asia-Pacific, Middle-East and Africa
WHONET, National surveillance networks around the world	Many gram-positive and gram-negative bacterial species	Worldwide

## Appendix I

### Glossary

**Antibacterial:** a drug that kills or inhibits the growth of bacteria

**Antibiotics:** a class of substances that can kill or inhibit the growth of some strains of bacteria; examples are penicillin, tetracycline, erythromycin and cephalosporins

**Antibiotic resistance:** the ability of microorganisms to resist inhibition by antibiotic substances; antibiotic resistance is genetically determined and can occur through a variety of mechanisms

**Antibiotic susceptibility:** the opposite of resistance; applies to bacteria (or other microorganisms) that are killed or inhibited by an antibiotic; susceptibility to a particular antibiotic does not mean that the microorganisms are susceptible to all antibiotics

**Antimicrobials:** a class of substances that can destroy or inhibit the growth of microorganisms, such as bacteria, fungi, and parasites

**Beta-lactam antibiotics:** the most widely used class of antibiotics, which includes penicillins, cephalosporins, carbapenems, and monobactams; beta-lactam antibiotics act by inhibiting the ability of a microorganism to make its own cell wall, thereby killing the organism

**Beta-lactamase:** an enzyme produced by some bacteria that degrades beta-lactam antibiotics, rendering them ineffective as treatments

**Broad-spectrum antibiotic:** an antibiotic effective against a large number of bacterial species (or species of other organisms)

**Empiric therapy:** antibiotic treatment based on signs and symptoms of disease and in the absence of definitive test results from the clinical diagnostic laboratory

**Extended-spectrum beta-lactamases (ESBLs):** enzymes that destroy a certain class of antibiotics called beta-lactams; beta-lactams have been used effectively over the years to treat serious hospital infections

**Isolate:** a pure culture of a microorganism

**MDR-TB:** multi-drug-resistant tuberculosis

**Methicillin-resistant *Staphylococcus aureus* (MRSA):** strictly speaking, a bacterial strain resistant to methicillin; in practice, MRSAs are generally resistant to many antimicrobials and some are resistant to all antimicrobials except vancomycin

**Microorganism:** a living organism that cannot be seen with the unaided human eye; examples include bacteria, some fungi and protozoa; viruses are sometimes included in this category.

**Multiple resistance or multiple drug resistance (MDR):** applies to bacteria (or other organisms) that are resistant to more than one antibiotic

**Narrow-spectrum antibiotic:** an antibiotic effective against a limited number of bacterial species (or species of other organisms)

**Nosocomial infection:** infection acquired during hospitalization that is neither present nor developing at the time of the hospital admission (unless related to prior hospitalization)

**Pathogen:** a microorganism or virus that is capable of causing disease

**Prevalence:** the total number of cases (new as well as previous cases) of a disease during a designated time period

**Susceptibility test:** any of a large number of tests to determine if an organism is susceptible or resistant to an antibiotic

## Appendix II

### Principles of appropriate antimicrobial use

From the standpoint of clinicians:

- Make accurate diagnoses.
- Use appropriate antimicrobial combinations.
- Consider use of a narrow-spectrum antimicrobial when disease agent is known.
- Avoid unnecessary antimicrobial use for viral infections, such as the common cold, and overuse for serious infections.
- If treating empirically, revise treatment based on patient progress and/or test results.
- Check up-to-date guidelines and local surveillance data.

From the standpoint of patients:

- Take antimicrobials exactly as directed.
- Avoid demanding antimicrobials against your clinician's advice.
- Take all medication prescribed, even if symptoms disappear, because if treatment stops too soon, some bacteria may survive and re-infect.
- Avoid request of specific antimicrobials from your clinician because the medication chosen needs to be tailored to the specific type of infection.

## Appendix III

### References

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2. World Health Organization. State of the World's Vaccines and Immunizations. Geneva, Switzerland (2002).
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## Appendix IV

### Other References

- Barza, M, Gorbach, S L., (Eds). The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences: A Report of the Facts about Antibiotics in Animals and the Impact on Resistance (FAAIR) Project-The Alliance for the Prudent Use of Antibiotics, *Clin Infect Dis* **34** (Suppl 3):S71-S144 (2002)
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## Appendix V

### Map References

For TB:

[http://www.who.int/gtb/publications/drugresistance/2004/drs\\_report\\_1.pdf](http://www.who.int/gtb/publications/drugresistance/2004/drs_report_1.pdf)

For *Neisseria gonorrhoea*:

<http://www.who.int/csr/drugresist/infosharing/en/>

For HIV:

Tang, JW and Pillay, D. Transmission of HIV-1 drug resistance. *J Clin Virol.* 30:1-10 (2004)

For malaria:

[www.who.int/csr/resources/publications/drugresist/malaria.pdf](http://www.who.int/csr/resources/publications/drugresist/malaria.pdf)

[www.rbm.who.int/amd2003/amr2003/amr\\_roc.htm](http://www.rbm.who.int/amd2003/amr2003/amr_roc.htm)



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