Executive Summary: Select Findings, Conclusions, and Policy Recommendations

The Alliance for the Prudent Use of Antibiotics

Summarized below are select findings from the articles that constitute the Global Antimicrobial Resistance Alerts and Public Health Implications: The 2005 Global Advisory on Antibiotic Resistance Data (GAARD) Report, A Project of the Alliance for the Prudent Use of Antibiotics (APUA).

ANTIMICROBIAL RESISTANCE IN *STREPTOCOCCUS PNEUMONIAE* [1]

- *S. pneumoniae*, the bacterium responsible for most cases of pneumonia, is increasingly resistant to traditional penicillin therapy and to newer macrolide antimicrobials.
- Global rates of penicillin resistance for *S. pneumoniae* range from 2.4% (Germany) to as high as 50.1% (South Africa).
- Macrolide resistance now exceeds penicillin resistance in some regions. Rates of resistance for *S. pneumoniae* range from 14.7% (Canada) to 88.3% (Vietnam).
- Global rates of fluoroquinolone resistance for *S. pneumoniae* are comparatively low (1%–18%) but are rising at an alarming rate worldwide.

ANTIMICROBIAL RESISTANCE IN *HAEMOPHILUS INFLUENZAE:* HOW CAN WE PREVENT THE INEVITABLE? [2]

- Resistance to ampicillin in *H. influenzae* 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 resistance patterns in the community for *H. influenzae* may mimic those found for *S. pneumoniae*. The potential for emergence of resistance to macrolide and fluoroquinolone classes is cause for concern.

THE GLOBAL STATUS OF RESISTANCE TO ANTIRETROVIRAL DRUGS [3]

- The introduction of HAART has changed the face of HIV/AIDS in resource-rich countries by dramatically reducing mortality and morbidity. These advances have translated only minimally to the developing world, where the impact of the epidemic is catastrophic.
- The success of HAART is increasingly threatened by the resistance of HIV 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 resistance in HIV at the global level, although a number of national and regional surveillance projects have been launched.
- Among the most representative data sets, the Combined Analysis of Resistance Transmission over Time of Chronically and Acutely Infected HIV Patients in Europe (CATCH) study has measured resistance in 17 European countries (during 1996–2002) and found a frequency of resistance of 9.6% to any drug class and upwards of 1.7% to $\geq$2 drug classes.

DRUG RESISTANCE HAMPERS OUR CAPACITY TO ROLL BACK MALARIA [4]

- Malaria is worsening, to a large extent because of the emergence and spread of parasites resistant to

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drug treatment. Continued use of failing drugs and inadequate treatment contribute to the growth of resistance to treatment and to increased morbidity and mortality due to malaria.

- 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 the neglect of development of drugs for malaria.
- 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 use of combination therapies.

GLOBAL EPIDEMIOLOGY OF ANTI-TUBERCULOSIS DRUG RESISTANCE [5]

- Multidrug-resistant tuberculosis has reached alarming and unprecedented levels in every corner of the globe. High concentrations of multidrug-resistant tuberculosis are found in eastern 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 levels of multidrug-resistant tuberculosis.
- Treatment of multidrug-resistant tuberculosis is much more complex and prolonged and is significantly more expensive than treatment of drug-susceptible cases of tuberculosis. Mortality is high as well.
- Control of tuberculosis is undermined by the HIV epidemic.
- The limited surveillance of nations with a high burden of tuberculosis, such as China and India, is worrisome, because it is suspected that the rate of multidrug-resistant tuberculosis is high in these areas.
- The strengthening of laboratory networks in conjunction with improved surveillance is essential to control of tuberculosis.

ANTIMICROBIAL RESISTANCE IN *NEISSERIA GONORRHOEAE* [6]

- 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.
- Multidrug-resistant gonorrhea from Asian countries where it is endemic 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 5 times that in those without gonorrhea. Persons with gonorrhea are also more susceptible to acquisition of HIV infection.

COMMUNITY-ASSOCIATED *STAPHYLOCOCCUS AUREUS* [7]

- Community-associated methicillin-resistant *S. aureus* (MRSA), which bears significant similarities to and differences from health care–associated 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, military personnel, and men who have sex with men.
- Proven, generalizable strategies and programs for prevention of the emergence and spread of community-associated MRSA are lacking.
- Further surveillance and epidemiological and clinical studies on community-associated MRSA infections are necessary for documentation of the extent of the problem and for development and evaluation of effective prevention and control efforts.

EXTENDED-SPECTRUM β-LACTAMASES [8]

- Extended-spectrum β-lactamases (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, which often leaves only limited treatment options as alternative choices.
- Antimicrobial resistance due to ESBL production is rapidly increasing. According to Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) data, 11%–30% of

strains tested *(Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis)* may be ESBL producers.
- To ensure effective treatment, laboratories should routinely test for the presence of ESBLs.

METALLO-β-LACTAMASES [9, 10]

- New types of metallo-β-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 United States in late 2002.
- Metallo-β-lactamases are usually harbored by species with intrinsic resistances, so that the enzyme genes can carry resistances to other antimicrobial classes, producing various multidrug-resistant strains for which there are no therapeutic options.

EVOLVING CONCEPTS OF PHARMACEUTICAL COMPANY–SPONSORED SURVEILLANCE STUDIES [11]

- Large, multiyear studies such as the Alexander Project are instrumental in tracing the evolution of antimicrobial resistance.
- Data from these studies can be used 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. Although 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 rates of resistance, as well as those with high rates. To date, little research has focused on areas with low rates of resistance, from which much could be learned.

ECONOMIC BURDEN OF DRUG RESISTANCE [12]

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: (1) costs for hospitalized patients infected with resistant bacteria are US >$20,000 (per patient) higher than the costs for patients infected with susceptible strains; (2) fear of resistance leads physicians to prescribe alternative, more costly drugs for the initial treatment of infections—the extra costs for treatment of ear infections alone exceed US $20 million annually; and (3) 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 to wear gowns and gloves increased costs by US >$70,000 annually in a single intensive care unit.

CONCLUSIONS

Antimicrobial resistance is a global pandemic that affects each person who contracts an 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. The following are among the most serious consequences.

- Multiresistant gram-negative bacilli are becoming untreatable, particularly with the mounting emergence of metallo-β-lactamases.
- Community-associated 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 throughout the developing world. Although alternative drugs are available, they are not affordable in countries most affected by malaria.

Without public attention and urgent action, drug resistance threatens to catapult the world back to a preantimicrobial 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 infectious diseases and drug resistance: we must wake up to the danger before it is too late.

It is clear 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 improve knowledge of the frequency of resistance, to promote appropriate use of existing antimicrobials, and to discover new drugs, diagnostic tools, 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 and 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 that the shadow of drug resistance is spreading across the globe. To forestall a total eclipse of effective treatment for infectious diseases, organizations and governments must provide a dramatic increase of funding for groups tracking and controlling drug resistance. These include the US Centers for Disease Control and Prevention, the US Food and Drug Administration, the National Institute of Allergy and Infectious Diseases, National Institutes of Health, the World Health Organization (WHO), the US Department of Agriculture, nonprofit academic organizations such as the Alliance for the Prudent Use of Antibiotics (APUA), and public/private partnerships such as GAARD (Global Advisory on Antibiotic Resistance Data). The WHO and the US government have developed plans to contain the growing threat of antimicrobial resistance. What is needed now is leadership and expanded resources to tackle the growing menace and restore the physician's certainty in treatment of infectious diseases.

MAJOR SURVEILLANCE AND CONTROL RECOMMENDATIONS FOR BOTH THE INDUSTRIAL AND THE DEVELOPING WORLDS

- Increase resources in both the industrial and developing worlds to curtail the spread of antimicrobial-resistant bacteria.
- Increase public and health provider education and awareness about the threat of antimicrobial resistance and need for more appropriate antimicrobial use.
- Support development and dissemination of cost-effective model interventions to improve antimicrobial use and contain resistance.
- Support national and international surveillance efforts and develop and expand laboratory capacity worldwide to improve monitoring of the frequency, emergence, and spread of antimicrobial resistance.
- Support research and development efforts and incentives to discover new therapeutic agents with novel modes of action to treat and control resistant infections.
- Support development of new vaccines and rapid diagnostics to minimize overuse of antimicrobials.
- Establish and promote cost-effective infectious disease treatment and control protocols that will foster prudent antimicrobial prescribing and dispensing practices and contain antimicrobial resistance.
- Aggressively promote access to and use of preventive measures, such as high-quality rapid diagnostics, infection control programs, and vaccination and appropriate-use campaigns.
- Improve antimicrobial use in both human medicine and agriculture, because there is transfer of resistant bacteria among human, agricultural, and ecological niches [13, 14].

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