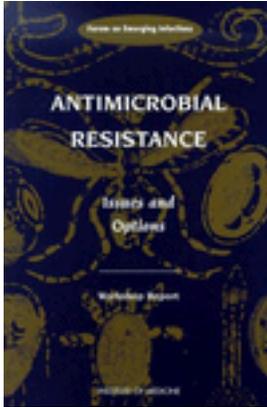


Free Executive Summary



Antimicrobial Resistance: Issues and Options

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Antibiotic resistance is neither a surprising nor a new phenomenon. It is an increasingly worrisome situation, however, because resistance is growing and accelerating while the world's tools for combating it decrease in power and number. In addition, the cost of the problem--especially of multidrug resistance--in terms of money, mortality, and disability are also rising. This book summarizes a workshop on antimicrobial resistance held by the Forum on Emerging Infections. The goal of the Forum on Emerging Infections is to provide an opportunity for representatives of academia, industry, government, and professional and interest groups to examine and discuss scientific and policy dilemmas of common interest that are specifically related to research on and the prevention, detection, and management of emerging infections. Organized as a topic-by-topic synthesis of presentations and exchanges during the workshop, the book highlights lessons learned, delineates a range of pivotal issues and the problems they raise, and proposes some simplified ideas about possible responses.

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Workshop Summary

INTRODUCTION

Antibiotic resistance as a phenomenon is, in itself, not surprising. Nor is it new. It is, however, newly worrying because it is accumulating and accelerating, while the world's tools for combating it decrease in power and number:

- More than 90 percent of *Staphylococcus aureus* strains are resistant to penicillin and other related antibiotics.
- There is an alarming rise in the incidence of enterococci (the streptococcus that is the most common cause of hospital-acquired infections) resistant to the antibiotic vancomycin, often the last weapon for defeating these pathogens.
- As many as 40 percent of strains of pneumococci in some parts of the United States are now partly or completely resistant to penicillin and a number of antibiotics.

The costs of these dynamics, especially multidrug resistance, is also rising—in terms of mortality, disability, and dollars. Antibiotic-resistant bacteria generate a minimum of \$4 billion to \$5 billion in costs to U.S. society and individuals yearly, and in 1992, the 19,000 deaths directly caused by hospital-acquired infections made them the eleventh leading cause of death in the U.S. population.

Also, because general confidence in the existing antibiotic toolkit had muted any sense of urgency, there has been a distinct lag in producing new classes of antimicrobials, despite great advances in the fundamental science that is fueling pharmaceutical innovation in many other areas. This situation is changing, and the pharmaceutical industry has in the past few years expanded its investment substantially, but public-sector investment awaits reinvigoration. What is needed now is sustained, sufficient support—for basic pioneering research, for the clinical research required to move truly new products from the laboratory to the pharmacy, and for the infrastructure underpinning both.¹

ISSUE AND OPTIONS

Beyond the fundamental question of resources, the workshop material indicated that the most critical issues have to do with the expansion, coordination, and improvement of the diverse elements of surveillance. There are also issues where relatively small but thoughtful investments could make a difference in what is known and what can be done about antimicrobial resistance, in research, clinical management and practice, and policy:

- answering questions around the *use of antibiotics in food production* (see page 4);
- emphasizing ways to *prolong the effectiveness of existing antibiotics* (see page 5);
- pursuing key areas of basic research and seeking incentives for *developing new antibiotics* (see page 6); and
- exploring *legal and regulatory mechanisms* in key areas of need (see page 7).

SURVEILLANCE

ISSUES: No country, including the United States, has a reliable, longitudinal, full-service antimicrobial resistance surveillance program with comprehensive focus, nor is there a comprehensive database for monitoring trends in antimicrobial usage. Research and information on the impact of rapidly increasing antimicrobial resistance in the community are lacking. Antibiotic use is widespread not just in hospital and community settings, but on the farm, yet knowledge of the magnitude of all these uses depends largely on estimation and extrapolation. Multiple surveillance activities around the globe are attempting in different ways and at different speeds to move toward the ideal depicted in this report, but these systems, as a group, are uncoordinated and unstandardized. Thus, the magnitude of the resistance problem and its impact are really unknown and may be considerably understated.

There are also many issues at the laboratory level. Some currently available molecular methods are clearly applicable only to research and reference laboratories; their feasibility for most commercial or clinical laboratories is limited. Also, in the United States, the critical National Committee for Clinical Laboratory Standards (NCCLS) Guidelines seem not to be as widely and regularly available as would be useful, and the processes and criteria for their development are not clear.

OPTIONS:

- Funding, implementation, assumption, or assignment of leadership, and formation of partnerships for implementing the 1995 American Society for Microbiology's detailed recommendations for a comprehensive resistance surveillance program.
- Improving data gathering and analysis, perhaps through national systems that would continuously monitor antimicrobial usage in hospital, community, and farm environments.
- Including information about the effects of resistance on the outcome of infections in data collection systems.
- Selecting and strengthening the laboratories in a set of sentinel hospitals as bases for global assessment of the prevalence and transmission of the most critical antibiotic-resistant genes, including training laboratory personnel in sentinel hospitals in standardized methodologies,
- Designing categories and pathways for reducing data sets into comprehensive packages for use by clinicians and researchers.
- Expanding distribution of NCCLS Guidelines and perhaps increasing the frequency with which they are updated.

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UNDERSTANDING THE USE OF ANTIBIOTICS IN FOOD PRODUCTION

ISSUE: Historically, there has been a paucity of data on the development and transfer of resistance produced by animal husbandry, aquaculture, and agricultural use of antibiotics, particularly solid quantitative data *with* well-described etiologic pathways and data on trends in antimicrobial usage in veterinary settings. Lack of ready access to data from veterinary reference laboratories has been a limitation in this regard.

OPTIONS:

- Collaboratively designed, implemented, and analyzed research on these dynamics, perhaps beginning with case studies (e.g., DT104, fluoroquinolones, gentamicin)
- Collaborative access to data from veterinary reference laboratories.

ISSUE: An ecological understanding could help in, a number of aspects of animal husbandry, including conditions that foster the enhancement of antimicrobial resistance.

OPTIONS:

- Systematic, collaborative development, by the United States Department of Agriculture, American Veterinary Medical Association, Food and Drug Administration, and producer organizations, of strategies and educational materials toward expanding such understanding.
- Developing cost-benefit and cost-effectiveness models of different on-farm antibiotic usages to enhance the public health community's understanding of farmer perspectives.

ISSUE: Applied research in Europe suggests potential in competitive exclusion therapies or "probiotics," the constructive use of harmless or beneficial colonizing organisms in different areas of food productions.

OPTION: Researching existing and unexploited literature and additional applied research.

PROLONGING ANTIBIOTIC EFFECTIVENESS

ISSUES: There are many needs related to the modification of attitudes and behaviors among providers, patients, parents, managed care organizations, and the pharmaceutical industry. Not the least of these is the need for ongoing education concerning infection control, hygiene, and sanitation in health facilities and in the community. Another involves standardization and application of guidelines for appropriate antibiotic use. However, many groups are compiling practice guidelines for antibiotic use, which may generate confusion and complicate their value for providers.

OPTIONS:

- Selecting and pursuing the alternative strategies listed in Table 5 of this report for interventions meant to modify attitudes, behaviors, and, where applicable, policies among the major parties to the antimicrobial resistance problem.
- Implementing a joint project involving all pertinent professional societies in developing unitary guidelines (including checklists for providers to use in clinical settings) for antimicrobial use, perhaps analogous to the Report of the Committee on Infectious Diseases of the American Academy of Pediatrics ("Red Book"), implementing their extensive dissemination, and very importantly, updating them periodically based on annual data from longitudinal studies.
- Expanding research into outcomes of antibiotic misuse, nonuse, and prudent use in health care facilities and in the community, as the foundation for the articulation and revision of guidelines, the policies of the health professions and the full range of health care facilities, and the formularies of such facilities, including the World Health Organization Essential Drugs List.

ISSUE: There are limited data available to describe the difference that prudent antibiotic use would make in the outcomes of infections and the prevalence of resistance. Without such data, public education and advocacy are constrained.

OPTION: Quantifying the risks of injudicious antimicrobial use and developing descriptive and predictive models of the differences that judicious use would make, to help in policy development, advocacy, and action.

ISSUE: Shorter courses of antibiotic therapy may in some cases be feasible and perhaps encouraged, with a positive effect on volumes of selective pressure.

OPTION: Designing and implementing research on clinical outcomes from shorter courses of therapy and different dosing regimens, as the basis for updating practice guidelines and revising labeling.

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DEVELOPING NEW PRODUCTS

ISSUE: There is said to be a perception in the pharmaceutical industry that collaborative development of new antimicrobials might be constrained by U.S. antitrust laws, although to what extent this is the case is unknown and the evidence is contradictory. On the one hand, both U.S. antitrust law and European Union competition law permit collaborative joint ventures within certain parameters; on the other, dispute about ownership if gene sequences is current and heated.

OPTION: Exploring the extent to which these factors really constitute disincentives to development of new antimicrobial products and, if this should prove to be the case, exploring alternative solutions for the dilemmas identified.

ISSUE: Resistance is so complex and dynamic at the genetic level that more work is *needed* to understand the diversity and prevalence of resistant gene families, both in nature and in the animal microflora that are the bridge to human contact, and to discern the origins of these genes and how they spread from one

OPTIONS:

- Studies of gene flow
- Using enrichment procedures and early-stage drug development to identify plasmids in the pertinent ecosphere that might become sources of resistance and their in vivo potential for "exchangeability" from natural sources

LEGAL AND REGULATORY APPROACHES

ISSUE: The Centers for Disease Control and Prevention (CDC) cannot mandate states to reform laws regarding reporting, but must rely on education, persuasion, and invitation.

OPTIONS:

- Exploring whether increased resistance and rapid diminution of effectiveness of existing antibiotics might justify awarding greater authority to the CDC to monitor and enforce legal duties regarding resistance, and consideration of the means by which this might be accomplished.
- Considering ways to integrate issues of resistance into formulary development processes.

ISSUE: Some existing products seem to have activity against resistant pathogens, but since this efficacy has not been documented, such indications do not appear in their labeling.

OPTIONS:

- Developing alternative ways to define efficacy—for example, surrogate markers, *in vitro technologies*, and *animal models*—to address the lack of well defined populations for clinical trials.
- Exploring the possibility of congressional authorization to extend patents for such products, and the relevance of recent legislation adding six months of exclusivity when the Department of Health and Human Services requests pediatric studies of an existing product, with the recognition that this topic is complex and difficult.

ISSUE: There is ambiguity as to whether requests for registration of antibiotics for use on agricultural products that *are exported* are governed by the environmental clauses or the food safety requirements of the North American Free Trade Agreement and/or the General Agreements on Tariffs and Trade. Nor does antibiotic resistance appear to be incorporated explicitly into discussions of food safety and the regulation and monitoring of imports.

OPTION: Collaborative dialogue, perhaps led by the World Health Organization and including representation from the World Trade Organization, European Union, and U.S. Departments of State and of Commerce.

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