ADDRESSING ISSUES OF ANTIMICROBIAL RESISTANCE

Approaches to Limiting Emergence of Antimicrobial Resistance in Bacteria in Human Populations

James M. Hughes and Fred C. Tenover

Infectious diseases continue to be major threats to human health around the world. Within the past few years, several divergent groups of organisms have emerged as significant causes of morbidity and mortality. Included among these are bacteria that are refractory to therapy because of the development of resistance to multiple antimicrobial agents. Multidrug resistance in strains of Mycobacterium tuberculosis, Streptococcus pneumoniae, Shigella dysenteriae, Salmonella typhi, and Enterococcus faecium has been reported. Surveillance of resistant microorganisms in the United States and abroad is fragmentary and targets relatively few organisms. Surveillance is further hampered by the fact that detection of some novel resistance mechanisms is difficult by means of current laboratory methods. Both clinicians and public health officials are likely to continue to face a variety of challenges regarding surveillance, treatment, prevention, and control of drug-resistant infections.

In 1962, Nobel laureate Sir McFarlane Burnet wrote, “One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious disease as a significant factor in social life” [1]. More recently, in 1988, another Nobel laureate, Dr. Joshua Lederberg, wrote, “The ravaging epidemic of AIDS has shocked the world. . . . We will face similar catastrophes again. . . . We have too many illusions that we can . . . govern the remaining vital kingdoms, the microbes, that remain our competitors of last resort for dominion of the planet” [2]. The experience of the past 20 years clearly indicates that Dr. Lederberg’s concerns are valid.

The Institute of Medicine Report: Emerging Pathogens

In the fall of 1992, the Institute of Medicine published a report prepared by an expert committee cochaired by Drs. Lederberg and Robert Shope [3]. The report, entitled Emerging Infections: Microbial Threats to Health in the United States, defined emerging infections as new, remerging, or drug-resistant infections whose incidence in humans has increased within the past 2 decades or threatens to increase in the near future. The committee identified six major factors that contribute to emergence of disease: changes in human demographics and behavior; advances in technology and industry; economic development and changes in land use; increases in international travel and commerce; microbial adaptation and change; and a breakdown of public health measures, as reflected by deterioration in the public health infrastructure at the federal, state, and local levels in the United States.

The decade of the 1990s has provided a number of examples of emergence and reemergence of disease, both in the United States and internationally. Striking domestic examples include foodborne disease caused by Escherichia coli 0157:H7 [4], waterborne disease caused by Cryptosporidium species [5], and hantavirus pulmonary syndrome resulting from exposure to infected rodents [6]. Internationally, cholera returned to Latin America for the first time in over 100 years [7], a new strain of Vibrio cholerae (V. cholerae O139) emerged in the Indian subcontinent [8], plague occurred in India [9], and dengue type 3 was identified in Latin America [10].

These events have generated considerable concern regarding whether the public health systems in the United States and abroad have the capacity to recognize and address such emergencies in an effective and timely manner. Public health systems have lost some of their effectiveness through the years as a result of complacency about the control of infectious diseases. A number of articles that have appeared in lay publications [11, 12] call additional attention to the challenges posed by infectious agents.

The Problem of Antimicrobial Resistance

The definition of emerging infectious diseases in the Institute of Medicine report includes drug-resistant infections, which have been on the upsurge for several years [13–15]. Recent

Reprints or correspondence: Dr. James M. Hughes, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mail Stop C-14, 1600 Clifton Road N.E., Atlanta, Georgia 30333.
Clinical Infectious Diseases 1997;24(Suppl 1):S131–S134
This article is in the public domain.
examples in the United States include the emergence of multi-
drug resistance in *Mycobacterium tuberculosis* [16], vancomy-
cin resistance in enterococci [17], and penicillin resistance in
pneumococci [18]. Internationally, examples include multi-
drug-resistant *Shigella dysenteriae* type 1 infection in Africa
[19], multidrug-resistant *Salmonella typhi* in India [20], and
multidrug-resistant cholera in Ecuador [21].

In the United States, antimicrobial agents are the second
most frequently prescribed category of drugs, and expenditures
incurred from antimicrobial resistance have been estimated to
be $4 billion annually [22]. Antimicrobial resistance has a
number of very important implications for clinicians caring for
patients; infection control practitioners monitoring health care
institutions; public health professionals responsible for infec-
tious disease surveillance; clinical microbiologists responsible
for detection of resistant strains; persons and organizations
providing continuous medical education for physicians; health
education specialists responsible for communicating public
health messages to the public; and individuals in government
and industry responsible for setting drug and vaccine develop-
ment priorities.

Surveillance Programs

National surveillance of drug-resistant infections in the United
States is extremely limited. Surveillance systems exist for drug
resistance in nosocomial pathogens and in community-acquired
*M. tuberculosis*, gonococci, and pneumococci; however, the na-
ture and scope of the systems differ dramatically. More than
200 hospitals currently participate in the National Nosocomial
Infections Surveillance (NNIS) System, which has been opera-
tional since 1970 and has provided valuable data on trends in
drug resistance in nosocomial bacterial pathogens [23].

In contrast, laboratory-based surveillance of drug resistance in
*M. tuberculosis* was discontinued in the mid 1980s when the inci-
dence of tuberculosis was decreasing; it had to be rees-
tablished in the 1990s when the resurgence of tuberculosis
and the increase in multidrug-resistant strains was recognized.
Surveillance for resistance in gonococci has been conducted
since 1988 at sentinel surveillance sites in clinics for sexually
transmitted diseases [24], and 13 laboratories have participated
in a small sentinel surveillance system for pneumococcal sero-
types and drug resistance since 1983 [25].

The NNIS system has provided information on trends in
methicillin resistance in *Staphylococcus aureus* infections,
which in the early 1980s emerged as a problem limited to large
medical school-affiliated teaching hospitals. More recently,
however, such infections have emerged in smaller teaching
hospitals and—most recently—in smaller, nonteaching hospi-
tals (figure 1) [26]. The NNIS system also facilitated recog-
nition of the emergence of vancomycin resistance in enterococci
causing nosocomial infections, first recognized in hospitals in
New York City [27] (figure 2). The problem was initially con-
fined to patients in critical care units, but recent NNIS data
indicate that patients in other units are also at increased risk
of such infections.

In contrast to the availability of data on trends in resistance
in nosocomial pathogens, data on the frequency and patterns
of resistance in community-acquired pathogens are extremely
limited. However, such data are critically needed by clinicians
and public health professionals. The incidence of otitis media
has increased dramatically since 1975, as reflected by the
number of physician visits for this condition [28], and pneu-
mococci are an important cause of this infection. Child day-
care center attendance has been shown to be a risk factor for
otitis media [29].

The proportion of young children cared for in licensed child-
care centers has increased since the 1970s [30]. Drug
resistance has emerged as an important problem in pneumo-
cocci associated with otitis media in children attending child-
care centers in different geographic areas [31]. These observa-
tions are not surprising, since child-care centers have features
in common with acute care hospitals, where resistance has
long been recognized to be a major problem. Both types of
institutional settings involve care for susceptible populations
under conditions conducive to person-to-person transmission
of infectious agents. In addition, persons in both types of insti-
tutions are subjected to increasing antimicrobial pressure, in the
form of both prophylaxis and treatment of existing infections.

A recent report from the sentinel network, providing data
on penicillin resistance in pneumococci, described isolates from
sterile sites in 544 persons in 13 hospitals in 12 states (obtained
between October 1991 and September 1992). A total of 6.6% of
the isolates were resistant to penicillin, and 1.3% demonstrated
high-level resistance. A total of 16.4% of isolates were resistant
to at least one antibiotic, and 5.9% were multidrug resistant.
Resistance was most frequently associated with *Streptococcus
pneumoniae* serotypes 6B and 23F [31]. In addition, limited
surveillance data indicate that the prevalence of high-level re-
sistance to penicillin in *S. pneumoniae* has increased from
0.02% in 1987 to 1.3% in 1991.

Laboratory Methods for Detecting Resistance

Effective surveillance depends on the availability of accurate
and reproducible reference methods. For antimicrobial suscep-
tibility testing, standardized methods that incorporate the use
of multiple quality-control strains have been developed by the
National Committee for Clinical Laboratory Standards
(NCCLS) in the United States and by other international orga-
nizations. Detailed procedures for agar and broth microdilution
testing [32] and disk diffusion testing [33] are available in the
United States and are updated annually.

While commercially produced tests to detect resistance are
validated initially with use of the NCCLS reference methods,
new mechanisms of resistance that arise after validation studies
may not be detected, especially if the commercial method is
not a true doubling dilution procedure. Thus, monitoring resis-
Figure 1. Graph showing increase in methicillin-resistant Staphylococcus aureus (MRSA) infections reported to the National Nosocomial Infections Surveillance System at the Centers for Disease Control and Prevention. The faint dotted line shows when the rate of MRSA crossed the 5% level (— = isolates from large teaching hospitals; —— = isolates from smaller teaching hospitals; — — • — = isolates from nonteaching hospitals).

Figure 2. Graph showing the increase in percentage of vancomycin-resistant enterococci in intensive care units (I) and nonintensive care units (III), as reported to the National Nosocomial Infections Surveillance System at the Centers for Disease Control and Prevention.

Resistance in clinical laboratories alone may yield underestimates of resistance levels in a community, depending on the test method used. For example, the two automated systems of antimicrobial susceptibility testing (MicroScan [Baxter Laboratories, West Sacramento, CA] and Vitek [bioMérieux Vitek, Hazelwood, MO]) have difficulty in detecting vancomycin resistance in enterococci [34, 35]. These methods are widely used in the United States and Europe.

Thus, some outbreaks of vancomycin-resistant enterococci may go undetected unless alternative methods are used for susceptibility testing. Problems in detecting resistance to extended-spectrum β-lactamases in Klebsiella pneumoniae and E. coli by means of automated susceptibility testing methods also have been reported [36]. In addition, traditional broth microdilution methods are difficult to use for detecting penicillin resistance in pneumococci [37]. Although antibiotic gradient methods, such as the Etest (AB BIODISK, Solna, Sweden), have proved to be accurate and relatively easy to use [38, 39], they are also expensive. Improved laboratory methods are needed to enhance surveillance for emerging resistance in clinical laboratories.

Monitoring and Control of Emerging Pathogens

The Institute of Medicine report on emerging infections contained 15 recommendations focused on improving the ability to recognize and address in a timely way these emerging infectious disease threats. Because over half of the recommendations were directed at the Centers for Disease Control and Prevention (CDC), the agency undertook the development of a CDC strategy for addressing these threats. This strategy, entitled Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States, was developed with input from many experts in public health, microbiology, and clinical infectious diseases and was published in the spring of 1994 [40].

The introduction of the report states, "The magnitude of the problem of antimicrobial drug resistance is unknown, and global surveillance is fragmentary." The CDC plan addresses drug resistance in various bacteria, viruses, fungi, and protozoa (table 1). The plan highlights problems in institutional and community settings both in the United States and abroad.

The plan contains four goals that focus on strengthening surveillance and response capabilities, addressing applied research priorities, developing and evaluating prevention and control strategies, and strengthening the public health infrastructure at the federal, state, and local levels and internationally. Under the surveillance and response goal, one objective
is to improve surveillance and rapid laboratory identification to ensure early detection of antimicrobial resistance.

Specific activities under this objective focus on monitoring trends, developing and evaluating diagnostic tests, and identifying risk factors for emergence of infections with drug-resistant organisms. In assessing research priorities throughout the plan, it is important to ask the question, "What do we need to know and what tools do we need in order to develop sound public health policies, strategies, and guidelines to address emerging infectious diseases?"

The plan also stresses the importance of critical partnerships with local, state, and territorial health departments, other federal agencies in the United States (e.g., National Institutes of Health, U.S. Food and Drug Administration, U.S. Department of Defense, U.S. Department of Agriculture, and the Environmental Protection Agency), other public and private organizations, industry, academic institutions, ministries of health in other countries, and the World Health Organization.

### The Public Health Infrastructure and Monitoring of Resistance

Regarding infrastructure needs in the United States, a survey conducted in early 1993 by Dr. Michael Osterholm, then president of the Council of State and Territorial Epidemiologists, noted that >95% of the $42.2 million of federal resources provided to state and local health departments in 1992 for surveillance were allocated to four categorical disease areas (HIV/AIDS, other sexually transmitted diseases, tuberculosis, and selected vaccine preventable diseases). A total of $1.5 million was provided for surveillance of all other infectious diseases; <$10,000 was provided for surveillance of drug-resistant infections (Michael T. Osterholm, Ph.D., personal communication). When state and local contributions are considered, a total of $55,000 was allocated to support surveillance of drug-resistant infections.

That this approach is shortsighted is suggested by Berkelman and colleagues [41], who wrote, "History has shown us repeatedly, in terms of both human suffering and economic loss, that the costs of preparedness through vigilance are far lower than those needed to respond to unanticipated public health crises."

With reference to surveillance of antimicrobial resistance, a partnership is clearly needed to ensure effective surveillance. Such a partnership must involve clinicians, clinical microbiologists, epidemiologists, and public health laboratory personnel. Communication channels must be clear, and data must be shared among these individuals in a timely manner so that clinicians and public health professionals are aware of patterns and trends in resistance and have the opportunity to recognize emerging problems.

In addition to surveillance, strategies for controlling antimicrobial resistance include implementation of effective infection control precautions in institutional settings, rational use of antimicrobial agents, availability of rapid diagnostic tests, new drug development, and vaccine development. A workshop was held at the Rockefeller University in 1993 to discuss these strategies [42].

Recommendations from this workshop stressed the need to increase professional awareness of the problem of drug resistance, increase funding for basic research on mechanisms of resistance, improve the surveillance of resistance, and increase the availability of new drugs. The situation is urgent. It is noteworthy that only two new antiinfective drugs were approved in the United States in 1994; both (famciclovir and stavudine) are antivirals [43].

### Additional Challenges for the Future

It is important to consider what additional challenges the future may hold. There is clearly a need for data on patterns of drug resistance in HIV-infected persons. The recent widespread use of prophylactic tetracycline in India during the plague outbreak resulted in a dramatic increase in selective pressure during the short period of prophylaxis. Other issues recently under consideration in the United States include possible over-the-counter availability of topical erythromycin and oral acyclovir and the addition of quinolone antibiotics to animal feeds for therapeutic purposes. Each of these proposals, if approved, would result in additional increases in antimicrobial selective pressure.

### Conclusions

It is important to emphasize that (1) infectious diseases are important and increasingly complex clinical and public health problems; (2) prevention and control strategies will require application of sophisticated epidemiological, behavioral, and statistical approaches as well as new molecular biology–based technologies in the laboratory; and (3) integration of epidemiological, laboratory, and behavioral sciences is critical to the
prevention and control of emerging infectious diseases. We can be certain that we will continue to confront new and difficult challenges posed by drug-resistant infections.

References