

Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era

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In the last several years, the frequency and spectrum of antimicrobial-resistant infections have increased in both the hospital and the community. Certain infections that are essentially untreatable have begun to occur as epidemics both in the developing world and in institutional settings in the United States. The increasing frequency of drug resistance has been attributed to combinations of microbial characteristics, selective pressures of antimicrobial use, and societal and technologic changes that enhance the transmission of drug-resistant organisms. Antimicrobial resistance is resulting in increased morbidity, mortality, and health-care costs. Prevention and control of these infections will require new antimicrobial agents, prudent use of existing agents, new vaccines, and enhanced public health efforts to reduce transmission.

In an article published in 1982, Walsh McDermott described a typical medical ward in a large city hospital circa 1930. In contrast to the wards of the early 1980s, which were filled with patients with cancer, heart disease, or the complications of diabetes or hypertension, the wards of the pre-antimicrobial era were populated by patients with pneumonia, meningitis, bacteremia, typhoid fever, endocarditis, mastoiditis, syphilis, tuberculosis, and rheumatic fever. There were few effective therapies for most of these conditions. Many of the patients were young, and most would die of the disease or its complications. But within a few years, many of these bacterial infections, and particularly the complications, were rapidly to become memories of the pre-antimicrobial era. The introduction of antimicrobial agents in the mid-1930s "heralded the opening of an era in which literally millions of people—children, adults, and the elderly, all slated for early death or invalidism—were spared . . ." (1, p. 307).

The development and use of antimicrobial agents was one of the most important measures leading to the control of bacterial diseases in the 20th century. Other medical advances, such as vaccines and effective public health programs, were also instrumental, as were societal improvements in sanitation, hygiene, nutrition, and standard of living, all of which had already led to decreases in many infectious diseases before the advent of antimicrobial therapy. Nevertheless, antimicrobial therapy provided physicians with the ability to prevent some infections, to cure others, and to curtail the transmission of certain diseases. Today, the concept of an untreatable bac-

terial disease is foreign to most physicians in the developed world. Many bacteria remain fully susceptible to commonly used antimicrobial agents.

Despite this half-century of success, periodic warnings have recurred: the introduction of a new drug was almost always followed by resistance. But there were always newer drugs. Recent events, however, have questioned the continued general effectiveness of antimicrobial agents. The emergence of multiple-drug resistance in *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus*, *Shigella dysenteriae*, and *Plasmodium falciparum* has made many currently available antimicrobial drugs ineffective and in certain instances is already posing important public health problems. Furthermore, scientists at a recent National Institutes of Health workshop reported that fewer new antimicrobial drugs were under development (2). Such issues have raised the concern that we may be approaching the post-antimicrobial era. In this article, I will focus on bacterial infections and examine recent trends in the frequency of antimicrobial resistance, epidemiologic factors influencing these trends, the impact of antimicrobial resistance, and the implications for public health.

Sources of Data on Antimicrobial Resistance

Data on the epidemiology of antimicrobial resistance are drawn from three general sources: surveillance, outbreak investigations, and prospective studies. In a few instances, data on antimicrobial resistance are collected as part of a surveillance system. Such data are helpful in identifying trends in the frequency of antimicrobial resistance but are limited in being able to

elucidate the factors associated with the emergence, persistence, and transmission of antimicrobial-resistant bacteria. Information on such factors has usually been obtained from outbreak investigations or carefully designed prospective studies. Surveillance data are often neither comprehensive nor representative. Surveillance data for antimicrobial resistance are often incompletely reported and affected by a number of potential biases. For example, a specific clinical laboratory may report data that only represent the situation in that hospital. Reference laboratories may report the frequency of antimicrobial resistance for organisms that are submitted from a variety of sources for reasons that may have little to do with antimicrobial resistance, such as serotyping or other tests for identification. Thus, these collections may or may not be representative samples of the organisms causing disease. To address such problems, efforts have increased in recent years to develop reporting from multiple hospitals, to stimulate international data collection, and to establish active population-based surveillance to obtain more accurate and representative data. Unfortunately, much of this effort is still developmental and the data are limited.

Extent of the Problem

In examining human infections produced by drug-resistant organisms, it is convenient to consider the hospital and the community as separate ecosystems. Although somewhat arbitrary, this division reflects different populations, selective pressures, reservoirs, and other factors that are important in the emergence, persistence, and transmission of antimicrobial-resistant organisms. However, these ecosystems are not isolated from each other, and there are ample opportunities for the exchange of drug-resistant genes and organisms (3). In both ecosystems, antimicrobial resistance is a clinically important and apparently an accelerating problem (Fig. 1).

Nosocomial infections. Much of the attention on antimicrobial resistance has been focused on nosocomial or hospital-acquired infections. Hospitals have experienced periodic episodes of antimicrobial resistance affecting a variety of organisms, beginning with the emergence of penicillin-resistant staphylococci in the early 1950s. Subsequent

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nosocomial problems have included the emergence of various resistant Gram-negative organisms, methicillin-resistant staphylococci, and most recently vancomycin-resistant enterococci and multidrug-resistant *M. tuberculosis*. There are other organisms, such as multidrug-resistant salmonellae, that produce important nosocomial problems, primarily in the developing world (4). Nosocomial infections caused by drug-resistant organisms pose an important problem.

In the 1970s and 1980s, a number of outbreaks of methicillin-resistant staphylococcal (MRSA) infections were reported in various parts of the world, including the United States (5). Epidemic MRSA infections have become endemic in many hospitals and have been notoriously difficult to control. MRSA infections have spread from large tertiary-care teaching hospitals to smaller community hospitals and residential care facilities (6). These resistant organisms are causing bacteremias, pneumonias, and surgical wound infections. Strains have various patterns of multiple-drug resistance, and many are susceptible only to vancomycin. The potential for the emergence of vancomycin resistance, which has already been recognized in other Gram-positive organisms, poses a serious public health dilemma. The initial enthusiasm for alternative drugs such as ciprofloxacin has waned as the rapid emergence of resistance to this drug has been observed (7).

A similar problem with nosocomial infections has been the emergence of resistant enterococci, which are causing bacteremias and urinary tract and surgical wound infections. Enterococcal infections are difficult to treat and have often required synergistic combinations of antimicrobial agents such as penicillins and aminoglycosides (8). There has been an increase in the occurrence of gentamicin-resistant enterococci (9) and now of vancomycin-resistant enterococci. The Centers for Disease Control (CDC) maintains a National Nosocomial Infections Surveillance System, in which an increase in the frequency of vancomycin resistance has been observed from 0.8% in 1988 to 4.0% in 1991 (10). The emergence of resistance to aminoglycosides and vancomycin has the potential for untreatable enterococcal infections.

Multiple antimicrobial resistance among Gram-negative organisms has been a long-term and well-recognized problem with nosocomial infections, affecting a variety of organisms in various hospitals. Resistance has been observed in multiple genera, including *Escherichia*, *Enterobacter*, *Klebsiella*, *Proteus*, *Salmonella*, *Serratia*, and *Pseudomonas*. These Gram-negative organisms cause a wide range of hospital-acquired infections, including bacteremias, pneumonias, and urinary tract and surgical wound infec-

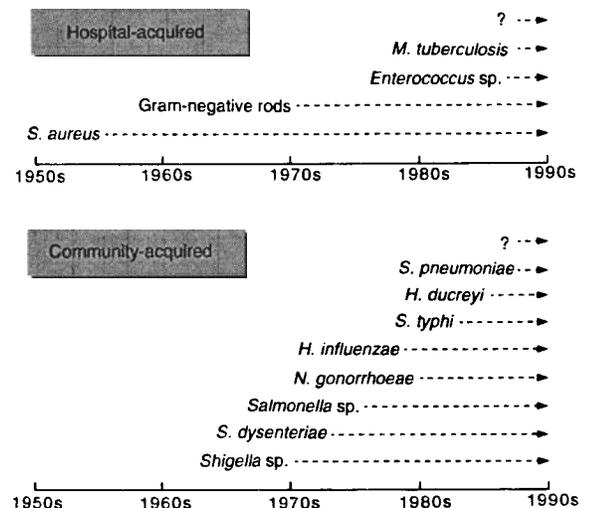
tions. In some instances, organisms are intrinsically resistant to certain antimicrobial drugs. In other instances, resistance has been plasmid-mediated and transferred among several genera even within a single hospital (11). Of recent concern are reports of two new groups of resistant Gram-negative bacteria—organisms with mutations in their outer membrane proteins that cause resistance by decreasing permeability for multiple antibiotics, and organisms that produce broad-spectrum β -lactamases (12, 13). This latter group of bacteria is able to inactivate a wide range of penicillins and cephalosporins, including many of the newer broad-spectrum cephalosporins. As yet, neither group of organisms has become a common problem.

A recent problem has been the emergence of multidrug-resistant tuberculosis (MDRTB). Although the problem is not restricted to nosocomial infections (correctional facilities have also been affected), these organisms have caused serious outbreaks in hospitals (14). This problem is discussed in greater detail in another article in this issue of *Science*. A number of infected persons have been coinfecting with the human immunodeficiency virus (HIV), but health-care workers and prison employees have also been infected and some have developed active disease. National surveillance for drug resistance is being reinstated by the CDC. In a one-time national sample of isolates from the first quarter of 1991, strains resistant to both isoniazid (INH) and rifampin had increased from 0.5% in 1982 through 1986 to 3.1% in 1991. Certain geographic areas are particularly affected. In a recent study in New York, 19% of isolates were resistant to INH and rifampin (15). Certain MDRTB strains are resistant to the most effective antimycobacterial drugs, leaving few options for either preventive or curative treatment.

Community-acquired infections. As in the hospital, a number of community-acquired bacterial pathogens are also developing increasing antimicrobial resistance. Antimicrobial resistance in community-acquired organisms occurs when organisms are transmitted from hospitals or farms but also emerges within the community itself in response to selective pressure of antimicrobial use. Resistant organisms can also be transmitted between communities. This has been particularly true in recent years as travel and international commerce of foods have lowered many of the barriers to international transmission of drug-resistant organisms. Several drug-resistant community-acquired organisms have become public health problems. These organisms are transmitted by a variety of routes and include enteric organisms transmitted by the fecal-oral route such as *Shigella*, foodborne pathogens such as *Salmonella*, sexually transmitted organisms such as gonococci, and respiratory pathogens such as pneumococci and *Haemophilus influenzae*.

Shigellosis has become an important problem affecting native American populations, children in day-care, and homosexual men. Although most cases of shigellosis do not require antimicrobial therapy, drug treatment is frequent. Historically, resistance emerges rapidly, is plasmid-mediated, and often is against multiple drugs. Transferable drug resistance was, in fact, first described in *Shigella* in the early 1960s (16). A study in 1986 demonstrated that 32% of a sample of *Shigella* isolates in the United States were resistant to ampicillin and 7% to trimethoprim-sulfamethoxazole—two drugs that were frequently used in the treatment of shigellosis (17). This study also demonstrated an epidemiologic association between trimethoprim-sulfamethoxazole resistance and the acquisition of shigellosis during travel to foreign countries.

Fig. 1. Emergence of clinically important antimicrobial resistance in selected human pathogens, 1950 to 1990.



Resistance in *Shigella* limits the use of antimicrobial agents for the treatment of individual patients and control of the pathogen's spread. From the global perspective, however, emerging resistance in one particular *Shigella* species, *Shigella dysenteriae* 1A, poses a clear public health problem. This organism has caused epidemics of severe diarrheal disease in the developing world, with mortality rates in excess of 15%. In the late 1970s, an epidemic of *S. dysenteriae* infections was recognized in central Africa (18). This epidemic has ebbed and flowed over the last decade, spreading into neighboring geographic areas, and the epidemic strains have acquired increasing resistance. In 1990, an epidemic of *S. dysenteriae* infections occurred in Burundi, and the epidemic strain was resistant to all oral antimicrobial agents available in that country (19). Such resistance is important because the cost of alternative oral agents such as fluoroquinolones and the cost and difficulty of delivering parenteral antimicrobial agents in the developing world limit the use of the few drugs to which this organism is still susceptible.

Salmonellae are primarily transmitted by the foodborne route, particularly by foods of animal origin. This organism typically causes a diarrheal illness that lasts several days and does not require antimicrobial treatment. However, persons with enteric fever or extra-intestinal *Salmonella* infections and some of those who are very young, elderly, or have underlying diseases are treated with antimicrobial drugs. *Salmonella* is becoming increasingly resistant to various antimicrobial agents. Three prospective studies of *Salmonella* antimicrobial resistance were conducted by the CDC in 1979, 1984, and 1989. In 1979, 16% of *Salmonella* isolates were resistant to one or more of 12 antimicrobial agents, in contrast to 24% in 1984 and 32% in 1989 (Fig. 2) (20-22). Resistance in *Salmonella* has been linked to antimicrobial use in food animals (23).

One *Salmonella* infection, typhoid fever, requires antimicrobial treatment because the mortality rate without treatment approaches 10%. The causative organism, *S. typhi*, is transmitted by food or water contaminated by infected humans. Typhoid fever is primarily a disease of the developing world. As with *S. dysenteriae*, outbreaks of drug-resistant organisms have been reported (24). In one recent report from Pakistan, 20% of pediatric typhoid cases were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (25). Newer, but more costly, antimicrobial drugs are available to treat these resistant infections.

Another group of community-acquired infections that has undergone important changes in antimicrobial resistance is the sexually transmitted diseases, in particular

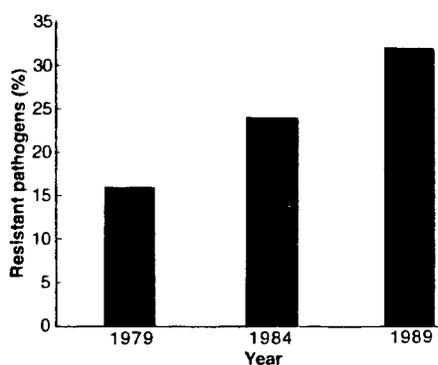


Fig. 2. Percentage of *Salmonella* isolates resistant to one or more antimicrobial agents in three prospective surveys conducted at 5-year intervals, 1979 to 1989

gonorrhea, which is caused by the bacterium *Neisseria gonorrhoeae*. Chromosomally mediated increases in penicillin resistance led to increased penicillin dosage requirements for the treatment of gonorrhea during the 1950s and 1960s. However, in the early 1970s the emergence of penicillinase-producing *N. gonorrhoeae* (PPNG) with plasmid-mediated penicillin resistance, and subsequent resistance to tetracycline in the 1980s, has necessitated the use of antimicrobials such as broad-spectrum cephalosporins and quinolones. Data obtained from the Gonococcal Isolate Surveillance Project demonstrate that from 1988 to 1990 the prevalence of PPNG increased from 3 to 10% and of tetracycline-resistant strains from 4 to 6% (26). Emerging resistance has also been observed in another sexually transmitted pathogen, *Haemophilus ducreyi*, the pathogen that causes chancroid. In a recent study of isolates from the United States and Thailand, strains were susceptible to broad-spectrum cephalosporins, but over 30% were resistant to erythromycin or trimethoprim-sulfamethoxazole (27).

Two community-acquired organisms transmitted by the respiratory route, *H. influenzae* type B and *S. pneumoniae*, are also showing greater antimicrobial resistance. At approximately the same time *N. gonorrhoeae* was acquiring resistance to penicillin, *H. influenzae* was developing resistance to ampicillin. *H. influenzae* is an important cause of invasive bacterial disease, particularly meningitis, in young children in both the developed and developing world. The emergence of ampicillin resistance led to modifications of the recommended treatment regimens for suspect *H. influenzae* meningitis. *H. influenzae* is one of the few organisms for which a population-based active surveillance system can monitor antimicrobial resistance. Data from this system indicate that, in 1986, 32% of *H. influenzae* isolates were resistant to ampicillin (28). At present, the broad-spectrum

cephalosporins are effective alternatives.

Of perhaps even greater concern has been the emerging resistance to penicillin in *S. pneumoniae*. This organism causes pneumonia and other invasive diseases, including meningitis, arthritis, and bacteremia. Pneumococcal disease affects persons in all age groups, but is particularly common in the elderly and the very young. It is an important cause of otitis media in young children. Although there have been occasional reports of isolated epidemics caused by drug-resistant pneumococci, recent reports suggest that the frequency of drug resistance is increasing (29). Pneumococci can be subtyped by a serotyping method. Certain serotypes are more commonly resistant. This may indicate that specific clones of drug-resistant pneumococci are being disseminated in various geographic areas. For example, a serotype 23F strain which led to outbreaks of disease in Spain has recently been recognized in several geographic areas in the United States (30). The emergence of drug resistance has serious consequences for the treatment of invasive pneumococcal disease. Strains resistant to penicillin also have decreased susceptibility to broad-spectrum cephalosporins which are frequently used in the empirical treatment of meningitis and other serious invasive bacterial infections.

The emergence of resistance in two other important respiratory pathogens, group A streptococcus and *Neisseria meningitidis* could be of particular concern. Group A streptococcus, which is the cause of streptococcal pharyngitis, rheumatic fever, and glomerulonephritis, has remained susceptible to penicillin. A recent report from Finland described an increase in erythromycin resistance in group A streptococci isolated from throat cultures from 7% in 1981 to 20% in 1990 (31). Such resistance eliminates an important alternative to penicillin. This rapid increase in resistance, coupled with the presence of penicillin resistance in other Gram-positive organisms, also suggests that penicillin resistance could emerge in group A streptococci. This would have serious implications for the treatment and prevention of streptococcal disease. In a similar way, the emergence of plasmid-mediated resistance in the gonococcus has raised concerns about the potential for the emergence of resistance in another *Neisseria* species, *N. meningitidis*. This organism causes meningitis and septicemia and is very likely to cause death if untreated. Meningococcal disease is endemic and epidemic in many parts of the world. At present, the meningococcus is susceptible to penicillin and chloramphenicol, the drugs of choice for treating this disease. The acquisition of transferrable resistance would be a very serious public health problem. An initial



report of a β -lactamase-producing *N. meningitidis* is particularly disconcerting (32).

The Impact of Antimicrobial Resistance

Antimicrobial resistance increases the morbidity, mortality, and costs associated with disease. Morbidity and mortality increase because effective therapy for specific infections is delayed. This is particularly true in instances where resistance emerges to the drug of choice for a specific infection or to the appropriate empiric therapy for a given syndrome. Because tests for antimicrobial susceptibility may take hours or days after the isolation of a specific bacterial agent, complications or death can result from antimicrobial resistance to generally accepted therapy. For example, during an outbreak of chloramphenicol-resistant *S. typhimurium*, an elderly woman died after several days of chloramphenicol treatment (33). At that time, chloramphenicol was considered the drug of choice for severe salmonellosis, and resistance to this particular agent was unexpected. In most instances, increases in morbidity and mortality occur early in the emergence of antimicrobial resistance and have been mitigated by the use of newer antimicrobial agents to which the organisms are susceptible. However, excess morbidity and mortality continue to occur when organisms develop resistance to most or all effective antimicrobial agents. Such has been the case with some of the resistant enterococci and is now being seen with multidrug-resistant tuberculosis (15). Also, increased morbidity and mortality will continue in instances where alternative antibiotics are too costly or cannot feasibly be administered, as in certain epidemics of resistant organisms in the developing world.

A recurring issue concerning the effect of antimicrobial resistance on morbidity and mortality is whether resistant bacteria are more or less virulent than susceptible strains of the same organism. The existing data do not show drug-resistant strains to be universally either more or less virulent than susceptible strains. Certain organisms may become debilitated and require an extremely susceptible host, whereas others may have an enhanced capability of infecting humans and causing serious disease. Some resistant strains grow less well in vitro. This observation has been explained by the excess DNA that might be present in plasmids that cause resistance or by mutations in important enzymes or proteins that might affect microbial structure or the acquisition of nutrients. Epidemiologic studies have also suggested that certain drug-resistant organisms require some selective advantage to cause disease. For some resistant *Salmonella* strains, prior antimicrobial exposure is

an important risk factor in the ability to cause salmonellosis (20, 34, 35). On the other hand, antimicrobial-resistant microorganisms can be more virulent. Several studies have demonstrated the coselection of virulence factors, such as adhesins or toxins on R plasmids present in drug-resistant organisms (36). Once disease is initiated, drug-resistant organisms are capable of causing severe infections. For some organisms the mortality rates of infections associated with drug-resistant strains are higher than those associated with susceptible strains (37, 38). It is likely that drug resistance results in a spectrum of effects on virulence.

One of the more important consequences of antimicrobial resistance is that resistance can lead to an increase in the incidence of the disease. This is most obvious for diseases in which antimicrobial treatment of ill persons or carriers is an important strategy in the prevention of additional cases of disease. Thus, a person infected with a multidrug-resistant strain of *M. tuberculosis* or *N. gonorrhoeae* who is not effectively treated will continue to pose a risk of transmission, in contrast to the patient infected with a susceptible strain for whom treatment prevents transmission.

A more subtle impact on the incidence of disease occurs when a person or animal receives an antimicrobial agent to which a potentially infecting or colonizing organism is already resistant. The antimicrobial drug, in part by killing competing organisms, provides a selective advantage that enables the resistant organism to cause disease, persist in the host for longer periods, or be spread more widely. When receiving subtherapeutic doses of tetracycline, animals excrete tetracycline-resistant organisms in their feces in larger numbers for longer periods and transmit the resistant organisms to other animals (39). In humans, exposure to an antimicrobial drug to which *Salmonella* organisms have already become resistant can convert asymptomatic infection to symptomatic infection and lower the infectious dose necessary to cause illness (23). These effects of antimicrobial use are also seen with other resistant organisms. In a recent pneumococcal outbreak in a day-care setting, carriers of a penicillin-resistant strain were more likely to have received long-term prophylaxis for recurrent ear infections (40). All of these effects can increase the likelihood of disease and enhance transmission.

The substitution of newer and more expensive antimicrobial agents for drugs to which organisms have become resistant increases the cost of medical care, as does the increase in morbidity associated with such infections (38). The estimated cost of treating a case of tuberculosis (including drugs, procedures, and hospitalization) increases from

\$12,000 for a drug-susceptible strain to \$180,000 for a multidrug-resistant strain (41).

Risk Factors for Emergence, Persistence, and Transmission of Antimicrobial-Resistant Bacteria

Epidemiologic studies have been undertaken to explain why resistance occurs at various frequencies in different ecosystems. These studies have identified a number of important factors that include microbial characteristics, environmental or human reservoirs in which resistance genes or resistant organisms can persist, patterns of antimicrobial use, and societal and technologic changes that affect the transmission of organisms. Various combinations of these factors determine the frequency of occurrence of drug-resistant organisms.

Certain microbial characteristics can apparently affect the frequency of antimicrobial resistance by enhancing the organism's ability to emerge, persist, or be transmitted. Such characteristics include the propensity to easily exchange genetic material, possess intrinsic resistance, survive varying environmental conditions, occupy certain ecologic niches, easily colonize, and infect (3). Thus, various combinations of these characteristics may explain why staphylococci, enterococci, or *Shigella* have relatively high frequencies of resistance. For example, the increase in resistance in the enterococci has occurred during the same time in which the use of broad-spectrum cephalosporins has increased in hospitals. Enterococci are intrinsically resistant to these agents, and thus in hospitals where these drugs are extensively used the enterococci have a selective advantage in colonizing patients or establishing reservoirs that would facilitate the acquisition of further resistance.

The presence of a reservoir is important in determining the frequency of antimicrobial resistance. A reservoir is an ecologic niche in which an infectious agent persists by a cycle of transmission or reproduction, or both (3). A reservoir can be a niche for an organism or a genetic element. Reservoirs provide an opportunity for the development of resistance, either by the exchange of genetic material with other drug-resistant organisms or simply by the persistence of an organism and exposure to the selective pressures that lead to development of resistance. Common plasmids have been detected in drug-resistant *S. aureus* and *Staphylococcus epidermidis* isolated from patients in the same hospital (42). In one such study, a strain of *S. epidermidis* with an antibiotic profile identical to that of the epidemic strain of *S. aureus* was isolated in the same hospital in the year preceding the *S. aureus* outbreak (43). Thus, the presence of drug resistance in the *S. epidermidis* res-

ervoir was important to the eventual emergence of drug-resistant *S. aureus*. Reservoirs also provide the opportunity for resistant organisms to persist and be transmitted, affecting the overall frequency of antimicrobial resistance. Reservoirs can be animate or inanimate, and their characteristics can affect the efficiency of transmission. In one MRSA outbreak, a specific patient was identified as a continuing reservoir for transmission to other patients (44). In some staphylococcal outbreaks in nurseries, transmission has been attributed to certain infants who disseminate large numbers of staphylococci and are referred to as "cloud babies" (45). Greater transmission leads to a higher frequency or prevalence of resistance.

Epidemiologic studies have repeatedly demonstrated the influence of antimicrobial use on the emergence, persistence, and transmission of antimicrobial-resistant bacteria. Antimicrobial use correlates with the frequency of resistance; it is not clear, however, that all types of antimicrobial use are associated with similar risks of resistance. Long-term use of antibiotics may pose a greater risk of antimicrobial resistance than short-term therapeutic or prophylactic use. In 1983, an outbreak of infection caused by a multidrug-resistant *Salmonella flexneri* occurred on a Hopi Indian reservation and was traced to a patient who had had recurrent *Escherichia coli* urinary tract infections and had been treated with long-term prophylactic trimethoprim-sulfamethoxazole (46). The combined laboratory and epidemiologic investigation of this particular outbreak demonstrated that, in this patient, the drug-resistant *S. flexneri* developed by acquiring an R plasmid from an *E. coli* that had emerged in her gastrointestinal tract during this prophylactic therapy. Subsequent cases of this multidrug-resistant *S. flexneri* occurred on the reservation. Thus, this outbreak was attributable to the selective pressure of this long-term prophylactic antimicrobial use. In animal populations, antimicrobial agents are used as short-term therapy to treat infections, but they are also used extensively in what are referred to as "subtherapeutic doses" in an effort either to prevent infections or to promote growth. These practices promote antimicrobial resistance in both animal and human pathogens (34, 47).

It is likely that certain microorganisms are becoming public health problems because a combination of technologic and societal changes are enhancing their transmission. In the community, technologic changes have facilitated both travel and the transportation of foods and thereby the importation of resistant organisms. On the other hand, the lack of technologic change in parts of the developing world has resulted in unhygienic and unsanitary conditions

that enhance the transmission of drug-resistant bacteria. These conditions may have a greater impact on the high frequencies of resistance of certain organisms in the developing world than the availability of over-the-counter antimicrobial drugs. In both the community and the hospital, another change has been the introduction of new broad-spectrum antimicrobial agents. These drugs are providing selective pressure to an increasing number and variety of microorganisms. Although the broad-spectrum nature of the drugs enables the physician to be more secure in the treatment of an undiagnosed infection, the effect of the extended spectrum may be a rapid enhancement in antimicrobial resistance in the hospital and community. Other changes in technology are also affecting the hospital. New technologies often provide different vehicles or modes of transmission for both drug-susceptible and drug-resistant microorganisms. For example, in one hospital, an epidemiologic investigation implicated the improper use of gloves in an epidemic of drug-resistant staphylococcal infections (48). In this outbreak, health-care workers were wearing gloves as part of universal precautions that were instituted to protect the employees against exposure to blood-borne infections.

Several societal changes are also enhancing the transmission of drug-resistant organisms. Demographic changes are increasing populations at risk for disease, including the elderly and the immunocompromised. The increase in day-care attendance has provided opportunities for increased infection, greater antimicrobial use, and consequently the transmission of drug-resistant microorganisms such as pneumococci, *Shigella*, and *H. influenzae*. A series of economic changes are enhancing the transmission of infectious diseases. Some of the advances in hygiene, nutrition, sanitation, and housing in the developed world have been eroded in specific populations, leading to crowding, homelessness, poor nutrition, and inadequate medical care; such conditions are conducive to the transmission of infectious diseases. Many of these factors have been implicated in the rising incidence of drug-susceptible and multidrug-resistant tuberculosis.

Economic changes have also influenced the erosion of the public health infrastructure within the United States. In many communities, eroding tax bases have led to a reduction in public health activities such as supervised therapy for the treatment of tuberculosis. The importance of this erosion is already evident in several metropolitan areas where the curtailment of tuberculosis control programs has been implicated in the increasing incidence of tuberculosis. Finally, behavioral changes are also

affecting the transmission of drug-resistant organisms. The changes in sexual activity that occurred in the 1960s and 1970s clearly contributed to the increased transmission of sexually transmitted diseases and likewise to the emergence of drug-resistant organisms. In the 1980s, increases in a variety of sexually transmitted diseases, caused by both resistant and susceptible organisms, have been associated with increased drug use, particularly of crack cocaine (49).

Prevention and Control of Antimicrobial Resistance

Several strategies are available to try to combat the public health emergency presented by antimicrobial resistance. As in the past, the development of new antimicrobial agents will continue. It is likely that new drugs for the treatment of multidrug-resistant tuberculosis will be manufactured, but it may not be feasible to produce the inexpensive and orally administered agents that would be needed to address the *Shigella* outbreaks in the developing world. The pharmaceutical industry cannot be expected to provide a limitless supply of new antimicrobial agents for resistant organisms. Even if a new class is discovered, it often takes 6 or 7 years to bring the new agent to market. In some instances, therapy with combinations of existing agents has been effective in preventing the emergence of antibiotic resistance. Although such therapy increases costs as well as the likelihood of allergic reactions, this might be a viable approach to preserving the effectiveness of certain agents.

New antimicrobial agents or combinations of existing antimicrobial agents, however, will continue to provide selective pressures, which in all probability will lead to the continued emergence of resistance. In contrast, an approach to reduce selective pressures for the development of resistance by more prudent use of antimicrobial drugs in humans and animals has been recommended (50). In this respect, efforts should be made to decrease inappropriate antimicrobial use in humans. Rapid diagnosis might reduce the use of inappropriate antimicrobial agents or enable the use of narrow-spectrum antibiotics. Shortening the duration of antimicrobial therapy or avoiding its long-term use might provide other ways of reducing antimicrobial resistance. It is also important to review the issue of antimicrobial use in animals in an effort to define those drugs and uses that are appropriate in animal populations. Equally important is the need for better surveillance to determine the true frequency of antimicrobial resistance so that studies can be specifically designed to explain and define the important factors in the emergence, persis-



tence, and transmission of drug-resistant organisms. Surveillance systems that are more sensitive and timely can provide information in making critical public health decisions.

Many of the above methods to reduce antimicrobial resistance focus on curative medicine, that is, preserving the ability to treat the ill or infected individual. Curative medicine is, in a sense, a failure of preventive medicine. As antimicrobial resistance increases, health efforts need to be focused on preventing transmission and infection rather than on treating the illness once it has occurred. A very effective mechanism for dealing with the emergence of antimicrobial resistance would be the development of vaccines to prevent diseases that are difficult to treat. There is also a variety of opportunities to disrupt transmission. In hospitals, infection control practices can be enhanced; in the community, hygiene and sanitation can be improved; and on the farm, a number of agricultural and animal husbandry practices can reduce the transmission of organisms between animals and eventually decrease their transmission to humans. The increasing frequency of resistance indicates the need for a stronger partnership between clinical medicine and public health. Unless currently effective antimicrobial agents can be successfully preserved and the transmission of drug-resistant organisms curtailed, the post-antimicrobial era may be rapidly approaching in which infectious disease wards housing untreatable conditions will again be seen.

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Tuberculosis: Commentary on a Reemergent Killer

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Tuberculosis remains the leading cause of death in the world from a single infectious disease, although there is little knowledge of the mechanisms of its pathogenesis and protection from it. After a century of decline in the United States, tuberculosis is increasing, and strains resistant to multiple antibiotics have emerged. This excess of cases is attributable to changes in the social structure in cities, the human immunodeficiency virus epidemic, and a failure in certain major cities to improve public treatment programs. The economic costs of not adequately addressing the problem of tuberculosis in this country are estimated from an epidemiological model.

In an interview on acquired immunodeficiency syndrome (AIDS) earlier this year with the Director of the National Institute for Allergy and Infectious Diseases (NIAID), a distinguished television newscaster asked, "How is it that we have conquered most infectious diseases but are unable to find a cure for AIDS?" The question reveals misperceptions that are costly to the public in both human and economic terms, and it is not a misapprehension solely of the general public. In

1969, the U.S. Surgeon General testified to Congress that it was time to "close the book on infectious diseases" (1). In fact, infectious diseases have not been eradicated but remain the largest cause of death in the world today, greater than cardiovascular disease or cancer (2). The World Health Organization (WHO) estimates that in 1991 there were still 4.3 million deaths in children from acute respiratory infections, 3.5 million from diarrheal diseases, 0.88 million from measles, and about 1 million from malaria (3). To that, one must add an estimated 1.5 million cumulative deaths worldwide from AIDS.

The stark reality, largely overlooked, is that among infectious diseases, tuberculosis (TB) is the leading cause of death (4). Each

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