Antibiotic Use and Resistance in the Community 3

The introduction of antibiotics nearly a half century ago controlled many life-threatening diseases, reduced the tolls of death and illness, and increased the life expectancy of Americans (Schlessinger, 1993). However, treatment with antibiotics can select for resistant bacteria that are not killed by the drugs, and those bacteria flourish and spread in environments where antibiotics are present (see chapter 2). As a result, bacterial resistance to antibiotics accompanied the use of the "wonder drugs," and some antibiotics lost their effectiveness in treating certain bacterial diseases. Antibiotic-resistant bacteria complicate treatment of illnesses ranging from ear infections to pneumonia and tuberculosis (TB). Patients infected with these organisms are more likely to require hospitalization, have a longer hospital stay, and die (McCaig and Hughes, 1995). Antibiotic-resistant bacteria are more common in hospitals, where antibiotic concentrations are high (see chapter 4), but they are also present in the community.

This chapter describes antibiotic use and resistance in the community, which in this report refers to those persons not in hospitals or nursing homes. The first section of this chapter discusses non-hospital use of antibiotics with an emphasis on physicians' office practice. The second section describes the populations that are most susceptible to antibiotic-resistant bacteria, the diseases to which they are most vulnerable, factors in the emergence of antibiotic-resistant bacteria, and changes in disease patterns related to or complicated by antibiotic-resistant bacteria. It also discusses the paucity of information about the prevalence of antibiotic-resistant bacteria as well as some surveillance systems used to obtain information about other infectious organisms.

INTRODUCTION

A mother takes her 2-year-old son to the doctor's office for a middle ear infection, also known as otitis media.[1] This visit is one of nine such visits over the past year. About every four to six weeks her son's physician switched antibiotics because the drugs had stopped working. She has had similar problems with her 4-year-old son, who has

[1] Otitis media is a bacterial disease that is prevalent in young children and more common in those in day care. Children in day-care are an at-risk population that are susceptible to all infectious diseases, some of which are caused or worsened by antibiotic-resistant bacteria. This issue is discussed further later in this chapter.

had about six ear infections during the same time period. This scenario is becoming more prevalent with increasing resistance to antibiotics. From 1975 to 1990, the annual visit rate to office-based physicians for otitis media more than doubled; for children under 15 years of age, the rate increased almost 150 percent (Schappert, 1992). Ninety percent of all American children will have had at least one ear infection before age six, and the national cost of treating them is $3.5 billion each year (Williams, 1994).

One of the causative agents in these recurring infections is *Streptococcus pneumoniae* ("pneumococcus"), which is a leading cause of illness and death in the United States, causing an estimated 7 million cases of otitis media; 50,000 cases of bacteremia; and 3,000 cases of meningitis annually. Scientists at the Centers for Disease Control and Prevention (CDC) and other researchers have documented increasingly common resistance to penicillin in *S. pneumoniae*. From 1979 through 1987, 0.02 percent of *S. pneumoniae* isolated from invasive infections were resistant to penicillin. By 1992, that percentage had jumped 60-fold to 1.3 percent. Resistance is much higher in some communities, where at least 30 percent of isolates are either intermediately or highly resistant to penicillin (Jernigan et al., 1995). Among the states, the highest documented penicillin resistance rate was 26 percent in Alaska, with rates in other parts of the country ranging from 1 to 16 percent (Tan et al., 1993).

Like antibiotic-resistant bacteria in general, penicillin-resistant *S. pneumoniae* are an international problem. They emerged in Australia and South Africa in the 1960s and 1970s. By the late 1980s, 40 percent of community-acquired and 95 percent of hospital-acquired *S. pneumoniae* infections in South Africa were penicillin-resistant. The strains spread rapidly and had been identified in Southeast Asia, other parts of Africa, and Europe in the 1980s. Hungary had the highest resistance rate in Europe in the late 1980s: up to 69 percent of *S. pneumoniae* isolated from children were resistant. In other countries, such as Spain and Romania, penicillin-resistance rates ranged between 22 and 44 percent (Klugman, 1990; Tan et al., 1993).

By the 1990s, some *S. pneumoniae* strains had become resistant to all penicillin-type drugs, as well as the aminoglycoside-type antibiotics, chloramphenicol, and erythromycin, leaving physicians with few treatment options, and causing epidemiologists to worry about when resistance to vancomycin—one of the last antibiotics available to treat some multidrug resistant organisms such as *Staph. aureus*—would emerge (Levine et al. 1991).

Antibiotic Use and Resistance

Any use of antibiotics, whether "appropriate" or "inappropriate," can contribute to the emergence and spread of antibiotic-resistant bacteria. Appropriate uses are those that benefit the patient, by treating a bacterial infection, and the risks of increasing the spread of antibiotic-resistant bacteria are offset by those benefits. Inappropriate uses are those that do not benefit the patient, but that increase the use of antibiotics and the risk of encouraging the spread of antibiotic-resistant bacteria. The term "overuse" is commonly used in reference to inappropriate use.

Numerous studies have shown a direct relationship between use of antibiotics and the spread of antibiotic-resistant bacteria (McGowan, 1983; Mouton et al., 1990; Moller, 1989; Ringertz and Kronvall, 1987; and Sogaard et al., 1974). Studies also indicate that reducing use of antibiotics may lower the frequency of antibiotic-resistant bacteria (Ballow and Schentag, 1992; McGowan, 1983). The focus in reducing antibiotic use has been on reducing inappropriate uses.

Resistant microbes would have emerged even if antimicrobial drugs were always used for the proper indication and at the proper dose and duration. However, the selective pressure would not have been as great, the pace of development of resistance would have been slower, and the extent of the problem in terms of the number of people involved would have been less. Once resistant strains are selected, they can infect other individuals and spread within a community or institution. They can also transfer the genetic information for resistance to other bacteria. While the natural history of the spread of antibiotic-resistant genes is not known with certainty and probably varies depending on the bacteria in which the mutation arose, the process can be described in a general way. Mutations occur and bacteria that bear them are selected by exposure to antibiotics. The frequency of the mutations may remain constant and low for many years and then spurt upwards, most likely as a result of the transfer of resistant genes among bacteria and the increased selection by antibiotic usage.

Factors in Prescribing Antibiotics

The most common infectious conditions seen in office practice are diseases of the respiratory system, nervous or sense organs (mostly otitis media in children), skin and subcutaneous tissue, and genitourinary system. In sum, these conditions account for more than 80 percent of office visits in which antimicrobial drugs are prescribed. Antibiotics are not only used to treat infections but to prevent them. Physicians prescribe antibiotics prophylactically to protect people who have been exposed to individuals with infectious diseases and to prevent commensal organisms—those bacteria that are naturally found in the digestive system or on the skin—from spreading as a result of disease or injury from their usual residence to normally sterile parts, the blood, tissues, and organs of the body. For example, penicillin may be administered prophylactically to patients who have damaged heart valves to prevent bacterial infections in the bloodstream and heart when they undergo dental or minor surgical procedures in dental or medical offices. (In-hospital prophylaxis is discussed in chapter 4.)

Many respiratory and ear infections are caused by viruses. Antibiotics have no effect on viruses, and there is no clinical evidence that antibiotics will prevent secondary or superimposed bacterial infections in a patient with a viral infection. Antibiotics prescribed for viral infections are wasted and are examples of inappropriate use and overuse. Moreover, some bacterial diseases will clear up in the same time with or without antibiotics. For instance, despite their widespread use for earaches, antibiotics do not always convey a benefit: about 20 percent of middle ear infections are caused by viruses. Perhaps one-third of them are caused by bacteria that cause self-limiting infections that will "go away" without treatment (Klein, 1994), although antibiotics may help them go away faster.

Physicians can obtain information about the causes of middle ear infections only by obtaining fluid samples from behind the patient's eardrum. Those samples are then sent to laboratories where the possible infecting organisms are cultured, identified, and classified as either susceptible or resistant to antibiotics (see chapter 6). These activities take several days, and often involve an invasive procedure, such as puncturing the eardrum to obtain a sample, which most physicians and patients want to avoid. The physician seeing a patient is not likely to wait several days for laboratory results before prescribing an antibiotic, and the patient is almost certainly not going to want to wait. Generally, the physician knows that there may be several types of bacteria that may be causing the infection. Therefore, he or she will usually prescribe a broad-spectrum antibiotic that will work against any of the several bacteria most likely to be causing the infection.

However, it would be preferable to treat patients with a narrow-spectrum antibiotic targeted at the specific cause of infection and save broad-spectrum antibiotics for the treatment of bacteria resistant to other antibiotics. But empiric treatment is the standard of care and, in some infections, the only possible course of action. Even so, some prescriptions are written with no more information than the patient's complaint or in response to the patient's request (see box 3-1).

Improvements in diagnostic technologies that would enable the rapid identification of bacteria and their patterns of antibiotic-susceptibility and resistance would reduce the need for empiric therapy. However, rapid technologies that would produce useful diagnostic results during the course of an office visit are not on the immediate

BOX 3-1: Misperceptions About Antibiotic Usage

An OTA staff member went to the doctor because of a persistent sore throat. The physician asked, "Want some antibiotics?" There was no physical examination, and the physician did not take a throat culture.

OTA staff understand the proper use of surveys and how they should be conducted to obtain data that are representative of the population. However, there are times when informal, non-scientific surveys can provide a snapshot of ideas and attitudes on a particular subject. The "Want some antibiotics?" event prompted a survey of all OTA staff by electronic mail to find out their attitudes toward antibiotic use. Of the nearly 200 OTA employees and contractors onsite, 95 responded. Here are some of the results: Within the past year, 59 percent of respondents or their family members had used antibiotics, with the most common conditions being ear infections, sinusitis, and upper respiratory infections. About half of the respondents, at one time or another, had requested antibiotics from their doctor, and 30 percent of the respondents indicated that a physician had offered them an antibiotic without an examination.

Most of those responding apparently understood the importance of taking all of their own prescribed antibiotics; 56 percent of the respondents indicated that they always completed their full course of prescribed antibiotics. One person reported that he did not complete his full course of antibiotics for an ear infection and stored the remainder of the prescription in his medicine cabinet because he felt better. He later had to reach into the cabinet for those same antibiotics because the ear infection got worse. This respondent's attitude toward "left-over" or "unused" antibiotics was common. Thirty-seven percent replied that they had later taken unfinished antibiotics that were stored in their medicine cabinets, and 10 percent said that they had taken antibiotics that someone else had stored in the medicine cabinet. Taking medicine prescribed for other persons is not only illegal, but it can have serious side effects.

Finally, most of the respondents were aware that antibiotics only work for bacterial infections and not colds, which are caused by viruses. But there were a few exceptions. Fifteen percent indicated they had taken antibiotics for a cold.

horizon. Moreover, to produce significant changes in antibiotic usage, the use of new technologies would probably have to be accompanied by changes in physicians' and patients' attitudes and expectations (see chapter 6).

Forces other than those created by the technical challenges of diagnosis influence and indeed promote the use of antibiotics. Antibiotics are sometimes referred to as the "drugs of fear" (Kunin et al., 1973) because they can be used to mitigate the physicians' fear of failing to provide patients with the very best care. Patients' fears of the unknown and expectations for rapid cure are fostered by exaggerated stories in the news media of dread diseases and new miracle cures. Pharmaceutical advertisements and sales representatives encourage "empiric, broad-spectrum coverage," perhaps glossing over the need for a full diagnostic assessment (Kim and Gallis, 1989; DiNubile, 1990). In addition, the physician may work for a health plan that prefers paying for antibiotics over paying for a test that may require another office visit.

Fundamentally, the risks, benefits, and costs of antibiotic treatment are not spread equally. The patient can expect to benefit from treatment with an antibiotic; there are few side effects from the antibiotics used in office practice, and out-of-pocket costs are likely to be relatively low. In the case where the antibiotic is not effective, and the patient recovers regardless, he or she has borne the very low risk of side effects and any out-of-pocket costs. The significant risks and costs of antibiotic use, including overuse, are borne by society as a whole. The contribution to antibiotic resistance from one person taking antibiotics is not that significant. Therefore, it might seem to a physician treating a specific patient that it is better to prescribe a broad-spectrum antibiotic, for example, than to wait for test results or for the infection to possibly clear on its own. However, collectively, these prescribing habits contribute to the spread of antibiotic-resistant bacteria. Nevertheless, the request for this study and the current attention given to antibiotic-resistant bacteria point to society's need to collectively alter the uses of antibiotics to preserve the efficacy of these drugs.

Trends in Antibiotic Use

A 1995 study of antibiotic use shows no change in the number of prescriptions for antibiotics, but indicates that older antibiotics, such as the penicillins, are being used less frequently in favor of the newer, more expensive drugs, such as cephalosporins (McCaig and Hughes, 1995). Currently, the most-used drugs are the new and expensive macrolides (azithromycin and clarithromycin), the fluoroquinolones (ciprofloxacin, ofloxacin, and others), and newer cephalosporins (cefuroxime, ceflacor, and cefixime) (Kunin, 1995).

Ciprofloxacin provides an example of the enthusiastic use of a new antibiotic among community and hospital physicians. Its low toxicity and broad-spectrum activity make it the primary choice for treating a wide range of conditions. Two years after its introduction in 1987, ciprofloxacin became the fourth most commonly prescribed antimicrobial at total sales value of $248 million (Frieden, 1990). This use may have contributed to the emergence of ciprofloxacin-resistant strains of MRSA (methicillin-resistant *Staph. aureus*), which is a common cause of serious infections in hospitals (see chapter 4)

POPULATIONS SUSCEPTIBLE TO ANTIBIOTIC-RESISTANT BACTERIA

Antibiotic-resistant bacteria pose a threat to the population as a whole but are more likely to cause illness in populations at greater overall risk of contracting infectious diseases. The following section examines those susceptible populations, the factors that contribute to their vulnerability, and the infectious agents to which they are most susceptible.

The Poor

The poor and those who do not have adequate access to sanitary living conditions or proper health care are particularly susceptible to infectious diseases. In underdeveloped countries most of the poor live in overcrowded urban areas, have poor hygiene, use unsanitary water, and have poor nutrition and inadequate waste disposal. Half of the city dwellers of developing countries, who are not classified as homeless, live in shantytowns and slums that, among other things, lack safe drinking water. Forty percent of them are without public sanitation or sewage facilities and a third live in areas in which there are no garbage or solid waste collection services (Garrett, 1994). As well illustrated by Levy (1992) and others, antibiotic-resistant bacteria that arise in foreign countries migrate to the United States when residents of foreign lands visit or immigrate here and when American citizens visit other countries and return with illnesses.

Even in this country, where sanitary standards are much better, other deplorable conditions exist. Many urban areas are laced with inadequate housing. Drug addiction, alcoholism, homelessness, incarcerations, and general economic impoverishment is a way of life for some inner-city residents, many of whom are ethnic minorities. These factors provide a ripe breeding ground for disease-causing organisms and the vectors that carry and spread them throughout the population.

People Without Adequate Health Care

Approximately 37 million Americans do not have medical insurance, and most of them are the working poor and their dependents (Hammond, 1994). Because this population generally cannot afford health care, many of their medical conditions go undiagnosed, or they may delay treatment because they have to choose between meeting basic living expenses and living with an illness that they think is not severe or life-threatening. Those who are poor, uninsured, and without a regular physician delay seeking medical care 40 to 80 percent more often than other patients; most think their problems are not serious. Overall, patients who are poor or uninsured are 12 times more likely than other patients to delay seeking health care because of cost (Weissman et al., 1991).

A 1992 OTA study confirmed this phenomenon. The report analyzed American studies on the relationships between having health insurance and individual health outcomes and found that, all other being essentially equal, uninsured people were up to three times more likely than privately insured individuals to experience lower health care utilization, potentially inadequate health care, and adverse health outcomes (OTA, 1992). These delays can worsen medical conditions and allow contagious diseases, like TB, to spread. Hospital stays of patients who reported delays in seeking medical care are 9 percent longer than hospital stays of other patients (Weissman et al., 1991). Once hospitalized, the patient may be at higher risk of a nosocomial infection (hospital-acquired infections) because the delay in treatment has lowered the body's natural resistance.

Lack of adequate medical care may have contributed to an outbreak of multiply resistant pneumococcal infections in Oklahoma in 1989 to 1990. Among the hardest hit were infants, the elderly, and the state's poor African American population, whose overall rate of disease was 60 percent higher than in whites. Overall, more than 15 percent of the patients who developed the pneumonia died (Haglund et al., 1993).

The Incarcerated

During the 1980s, the United States' "War on Drugs" produced a 126 percent increase in drug-related arrests (Skolnick, 1992). Most federal and state prisons were not equipped to handle this sudden onslaught of prisoners, many of whom came from disadvantaged backgrounds and did not have a history of adequate preventive health care (Anderson, 1990). Almost one-third of the newly admitted inmates in New York State reported having been homeless just before incarceration, and the majority of inmates had histories of substance abuse (OTA, 1993). These individuals are at high risk for infections, especially for TB and pneumococcal diseases, because both are diseases spread by airborne transmission and can move easily through badly ventilated, overcrowded areas (Anderson, 1990; Hoge et al., 1994).

Additionally, the inmate population is transient and provides a constant flow of people and their infectious organisms between the prison and the community. As many as half the inmates detained in a large New York City correctional complex, for example, are released within the first 48 hours after admission (Chisolm, 1988). Of the 15,000 to 20,000 or more inmates on any given day at Riker's Island, a correctional facility in New York City, half are discharged within a week (Navarro, 1993; Bellin et al., 1993). Although the National Commission on Correctional Health Care recommends that medical screening or a review of the medical screening of a prisoner's health be performed on or before the 14th day after initial booking, many prisoners are not screened or treated for asymptomatic communicable diseases. In Los Angeles County, for example, the average stay is less than 14 days. Even when screening is performed, the results may not be available until after the inmate has been released. Subsequently, those at risk may not be located and treated (Cohen et al., 1992).

The lack of adequate screening can result in dire consequences, not only for the inmates but to the community in which they are released, as well as for the workers at correctional facilities. From 1990 to 1992, 11 outbreaks of multiple-drug-resistant TB occurred in correctional facilities in 8 states, killing 13 inmates and one correctional officer. An outbreak in an Arkansas State prison spread to the community when a released inmate infected his wife and two children, one of whom died of probable tuberculous meningitis. Also, a news reporter covering the problems of overcrowding in urban jails became infected with TB after working on a story about a New

York City jail (Skolnick, 1992). Because of overcrowding, the lack of adequate screening, and the transient populations, TB has emerged in epidemic proportions in the nation's prisons. In 1988, the new case rate of active TB infection in the United States was 13.7 per 100,000, while the average rate was 75 per 100,000 among inmates of state and federal prisons. Some correctional facilities had higher rates. In 1991, Riker's Island in New York City had an active infection rate of 400 to 500 per 100,000 (Skolnick, 1992).

Prison overcrowding can also be a factor in the spread of pneumococcal disease among inmates. After two Houston, Texas, inmates died from pneumococcal sepsis on the same day, health officials uncovered an epidemic of pneumococcal disease, a rare occurrence in the era of antibiotics. The jail, which had been designed to house 3,500 persons, was accommodating 6,700 residents at the time of the outbreak. Over a four-week period, 46 inmates developed acute pneumonia or invasive pneumococcal disease. Besides overcrowded conditions, investigators also discovered that inmate susceptibility and inadequate ventilation for the number of inmates in the building were cofactors responsible for the outbreak. Although none of the strains of S. *pneumoniae* were resistant, the re-emergence of pneumococcal disease, coupled with sharp increases in the number of strains that are multiple-drug-resistant raises questions about the need for isolation wards in prisons and the vaccination of institutionalized persons at risk for pneumococcal disease (Hoge, et al., 1994).

The Homeless

Finding an accurate estimate of the homeless population is elusive. The estimates range from 192,000 to 3 million people. Regardless of the true number, the homeless are at greater risk for immune suppression because of poor nutrition, inadequate rest, and concurrent medical illness (Paul, 1993). Homeless shelters and shelters for battered women provide ideal conditions for transmission of infectious diseases, especially TB: large numbers of people in close quarters, poor ventilation, the presence of undiagnosed or untreated infectious cases, and prolonged exposure during lengthy stays, particularly in winter months. Several outbreaks of drug-resistant TB have emerged among the homeless in south Texas, New York, and Boston. Resistance rates in some of those areas were as high as 57 percent (Morris and McAllister, 1992; Pablos-Mendes et al., 1990; Barry et al., 1986; Gross and Rosenberg, 1987.)

Military Personnel

Military personnel in wartime field conditions live in close quarters, experience rudimentary food and water sanitation services, and have few opportunities to exercise good personal hygiene. Even peacetime training is characterized by crowding and confined quarters, which favor transmission of infectious diseases.

Historically, respiratory diseases are a common and serious problem in the military. As far back as 1500, historians recorded apparent streptococcal pneumonia epidemics. Recently, the U.S. military has experienced an increase in streptococcal-related disease. Outbreaks of *S. pyogenes* pharyngitis, acute rheumatic fever, and cases of streptococcal-induced toxic shock-like syndrome have caused concern among military health officials. Respiratory disease caused by the bacterium *S. pneumoniae* has also emerged as a problem. During the winter of 1989-1990, 124 Marine trainees developed pneumococcal pneumonia. Despite the Navy's administration of thousands of doses of pneumococcal vaccine and penicillin G to the troops, this Marine population continued to have the highest rates of pneumonia hospitalization in the Navy. In late 1991 and early 1992, a pneumonia outbreak on two U.S. Navy ships located in Italian waters afflicted 25 of the more than 1,700 crew members over a four-month period and killed two of them (Gray et al., 1994). These recent outbreaks, coupled with the emergence of drug-resistant strains of streptococci, could present increasing difficulties for military health officials and impede the military's performance.

Children in Daycare Facilities

An upsurge of women in the paid work force and the increasing number of single-parent families contribute to the increased use of daycare facilities. About 90 percent of families with preschool children use full- or part-time child daycare services (Thacker et al., 1992). As children spend more time in daycare, the risk for some infectious diseases has increased. Close physical contact, inadequate hygiene, and lack of toilet training facilitate the transmission of infectious agents within childcare settings. These agents are spread by the fecal-oral route, contact with skin, excretions, or bodily fluids, or transmission by aerosols or respiratory droplets. The two most common ailments for children in daycare are acute upper-respiratory tract illnesses and otitis media. By age two, children attending daycare have approximately seven or eight episodes of acute respiratory illness per year, which is 1.6 times greater than among children not attending daycare facilities (Thacker et al., 1992). Interpretation of these data is complicated because not all infections recognized in children in daycare are acquired in the daycare environment; some are acquired elsewhere but first recognized in the daycare facility (Sterne et al., 1986).

Many cases of drug-resistant bacteria have been reported in the daycare setting. One study showed that 57 percent of the children attending a particular daycare center were colonized with trimethoprim-resistant *Escherichia coli*, while another study detailed the hospitalization of two infants from the same daycare center in Texas, who had contracted sepsis and meningitis due to a multiple-resistant strain of *S. pneumoniae* (Fornasini et al., 1992; Rauch et al., 1990).

The Elderly

Although the elderly, those aged 65 and older, are a relatively small proportion of the population, their numbers are increasing. By the year 2025, the elderly will comprise a little more than 10 percent of the population (USBC, 1994). Almost all of the nation's nursing home population and a substantial part of the hospital population are elderly. Because of their diminishing immune systems, the presence of underlying diseases, and the use of invasive medical devices, the elderly are more susceptible to infectious organisms, including antibiotic-resistant bacteria (OTA, 1987). Hospitalized elderly patients are two to five times more likely to develop nosocomial infections than hospitalized younger patients. These infections are often fatal, in part because they are frequently caused by agents that are resistant to antibiotics. The elderly are susceptible to endocarditis, pneumonia, bacteremia, and bacterial meningitis, which is caused by *S. pneumoniae* in more than half the cases worldwide (Madhavan, 1994). (See chapter 4 for information about in-hospital disease, which is generally applicable to diseases in nursing homes.)

The Immunosuppressed

Immunosuppression, which is a result of a lowered immune system response, can be caused by a number of factors, including the following conditions:

- Prematurity (neonates);
- Inherited diseases;
- Malnutrition;
- Pregnancy;
- Concurrent infections;
- Severe trauma and burns;
- Infection with the human immunodeficiency virus (HIV);
- Malignancy;
- Radiation treatment;
- Immunosuppressive medications for transplantation, cancer chemotherapy, or treatment for autoimmune disease;
- Aging.

Immunosuppression can result in opportunistic infections in an individual who otherwise would have been able to fight illness. These infections are caused by typically non-threatening organisms that take advantage of a person's weakened state. Although opportunistic infections have received a great deal of attention over the past decade with the onset of the HIV pandemic, they are not new. It is well known that the very young and the elderly are at the greatest danger of succumbing to disease. Also, new medical treatments and invasive technologies have created additional openings for opportunistic pathogens (IOM, 1992). Therefore, drug-resistant bacterial infections can exacerbate health problems for the already immunocompromised.

FACTORS IN THE EMERGENCE OF BACTERIAL DISEASES

Global Accessibility

Travel involves the movement of people and microbes from one region to another and has always been a factor in the emergence of infectious disease. Whether new diseases emerge depends on the novelty of the microbe being introduced, its transmissibility, and the existence of an environment suitable for maintaining the disease and its agent. Therefore it is important to distinguish between transient introductions or acquisitions of new diseases, which occur frequently, and the establishment and propagation of a new pathogen, which occurs rarely (IOM, 1992).

For example, travelers from industrialized nations to developing countries may unknowingly transport virulent pathogens on their return. One traveler who smuggled South American crabs back to the United States was the origin of a cholera outbreak, and other infected travelers have brought the same disease to the United States from South America (Levine and Levine, 1995).

Improper Food Preparation Practices

Foodborne pathogens account for up to 7 million cases of foodborne illnesses yearly and in 1992 caused more than 9,000 deaths, most of which were associated with meat and poultry products contaminated by pathogenic micro-organisms (Cassell, 1995). Moreover, these estimates may be low because the surveillance systems for such diseases are passive, meaning they are based on voluntary reporting by state and local health departments.

Foods contaminated with pathogenic microorganisms can lead to infection and illness in two major ways. The first is by direct consumption of the contaminated food under conditions that allow the survival of the pathogen or its toxin, such as when a meat or poultry product is consumed raw or undercooked, or when products that are pre-cooked during processing are recontaminated before consumption (AMA, 1993).

For example, in 1982 a virulent bacterial strain, *E. coli* O157:H7, caused serious hemorrhages of the colon, bowel, and kidneys in 47 people in Oregon and Michigan (Riley et al., 1983). Nine years later an outbreak of *E. coli* in Massachusetts produced serious illness in 27 people, 10 of whom required hospitalization. Health officials traced the disease to batches of apple cider, which were made from apples on trees that were fertilized with livestock manure (Besser et al., 1993). In Washington State in January 1993, an E. coli outbreak caused severe illness in 144 people, many of whom ate undercooked hamburgers prepared by Jack-in-the-Box fast-food restaurants. A majority of the seriously ill were young children, who had to undergo kidney dialysis for weeks. Although media reports indicated that the outbreak killed four children, health officials could only link one of those deaths to the hamburger from the restaurant chain (Garrett, 1994).

The second method by which contaminated foods can cause illness is through cross-contamination in the kitchen or other food-handling areas. Salmonella bacteria, which can contaminate eggs, meat, and poultry, can cause severe but rarely fatal symptoms and are transmitted through improper food handling (Maurice, 1994). For example, when raw chicken or beef with a Salmonella-contaminated exterior contaminates a cutting board, countertop, kitchen utensil, or a person's hands, the bacteria can then come in contact with other foods, some of which are consumed raw, such as salad. Symptoms of Salmonella food poisoning are nausea and vomiting, followed by abdominal cramps and diarrhea, which last about three or four days, accompanied by fever in about half of the individuals infected. The most common source of Salmonella is food; only about 10 percent of transmissions are from person to person, and in some of those instances the ultimate source of the infecting organism was food (Cohen and Tauxe, 1986). Salmonella outbreaks have been reported in nursing homes and hospitals, particularly pediatric wards and nurseries, and on airline flights (Villarino et al., 1992; Hatakka and Asplund, 1993; Tauxe et al., 1987).

In addition to causing foodborne illness, many Salmonella are resistant to multiple antibiotics and are capable of transferring that resistance (Snydman and Gorbach, 1982; Lee et al., 1994). In 1983, the Minnesota State Department of Health discovered an antibiotic-resistant strain of *Salmonella newport* that caused six persons to be hospitalized for more than a week. Officials traced the outbreak to beef that had been fed low levels of antibiotics. All the bacterial strains found in the infected persons were resistant to penicillin, ampicillin, carbenicillin, and tetracycline (Garrett, 1994; Holmberg et al., 1984).

Sanitation and Hygiene

Improved public sanitation and personal hygiene practices have dramatically reduced the incidence of certain infectious diseases, especially in developed countries. The U.S. experience with cholera is an example of the success of such efforts. Between 1830 and 1896, the nation's major cities' populations swelled and produced crowded slums and fetid water and sewage "systems." These conditions caused a widespread death toll. In 1832, cholera killed thousands of New York City residents and during a three-month epidemic in 1849 claimed 10 percent of the population of St. Louis, Missouri. Reform was soon to follow. New York City officials, outraged by municipal filth, financed the construction of the Croton Aqueduct, which brought clean drinking water to the city for the first time. Eventually, the squalid slums were slowly upgraded, and subsequent outbreaks of the disease claimed fewer lives (Garrett, 1994). In contrast, in January 1991, cholera reached epidemic levels in South America for the first time in almost a century, demonstrating the health consequences of disruptions in sanitation. *Vibrio cholerae*, the bacterium that causes cholera, probably was introduced into the harbor at Lima, Peru, through the dumping of bilge water by a ship arriving from the Far East. Once in the water, the bacteria contaminated the fish and shellfish, which were then consumed by humans.

After causing these initial seafood-related cases in humans, the organisms probably were spread by fecal contamination of the water supply, which may have been inadequately chlorinated (IOM, 1992). In Latin America the epidemic raged well into 1994, and officials at the World Health Organization see no end in sight. As of 1995, Latin American governments have spent more than $200 billion for emergency repairs of water, sanitation, and sewage systems, according to the Pan American Health Organization. One of the substrains of the bacterium carried genes for resistance to the antibiotics ampicillin, trimethoprim, and sulfamethoxazole.

Clean water supplies and their protection from human and other wastes are fundamental public health principles in the United States. Where good sanitary practices are followed, many diseases that were once epidemic are successfully controlled. The same may be said for personal hygiene. Hand washing is effective in preventing the spread of many infectious agents. In addition, safe food-handling practices, including proper storage, cleaning, and preparation, have resulted in fewer cases of bacterial food poisonings. Also, the pasteurization of milk, which was instituted to prevent the transmission of bovine TB to humans, has been equally effective against other diseases such as brucellosis and salmonellosis (IOM, 1992).

The emergence of antibiotic-resistant bacteria, which makes bacterial disease more difficult to treat, increases the importance of sanitation and hygiene to prevent occurrences of these diseases.

Proper sanitation breaks the route of transmission, thereby bettering public health.

Inadequate Water Treatment and Inspection and Failing Infrastructure

Although the U.S. Environmental Protection Agency recommends that each state evaluate all components of its public water systems, most of them do not, according to a 1994 General Accounting Office report. The report found that 45 states did not perform the recommended evaluations, primarily because responsible state agencies lack sufficient funds for inspection and verification once problems are corrected (GAO, 1994).

In Missouri in the winter of 1989, a drug-resistant strain of *E. coli* in the drinking water supply killed two persons and hospitalized 32. The strain, which was resistant to sulfisoxazole, tetracycline, and streptomycin, was the first, and still largest, waterborne outbreak of *E. coli* and the first due to a multiple-resistant organism. The *E. coli* outbreak probably resulted from sewage contamination of the water distribution system. The bacteria survived and spread into the water system because there was no hyperchlorination to kill them (Swerdlow et al., 1993).

About two-thirds of the water systems in the United States are not disinfected, and many of them are in disrepair. The existence of antibiotic-resistant bacteria increases the risks from water systems that do not adequately control bacterial contamination, and outbreaks such as the one in Missouri may become more common. It is entirely possible that other waterborne outbreaks have involved antibiotic-resistant bacteria because there is no surveillance system from which to obtain accurate information.

CHANGES IN DISEASE PATTERNS

Sexually Transmitted Diseases

Transmission patterns of sexually transmitted diseases have changed a great deal in the last 20 years. In the 1980s, scientists initially recognized HIV as a sexually transmitted disease, and investigators discovered sexually transmitted etiologies for such diverse medical conditions as infertility, ectopic pregnancy, other adverse outcomes of pregnancy, anogenital cancers, and protocolitis—an inflammation extending from the rectum to the colon.

Also, syphilis re-emerged. Following World War II, the widespread availability of penicillin led to a 95 percent reduction of infectious syphilis in the United States. But after 1956, when the infection rate was four cases per 100,000, the incidence rose sharply to a 40-year peak of 20 cases per 100,000 in 1990. During this time period the target population for the disease shifted. From about 1960 to 1980, the disease targeted homosexual men, but during the last decade, the disease has had its greatest impact among minority heterosexuals as a result of the sex-for-crack cocaine epidemic. However, the incidence among minority heterosexuals involved in the trade is declining (Morse, 1995). The causative organism for syphilis, *Treponema pallidum*, remains completely sensitive to penicillin, and the re-emergence of this disease is not coupled with decreased treatment efficiency.

In contrast to syphilis, treatment of gonorrhea, which is caused by the bacterium *Neisseria gonorrhoeae*, has been complicated by rapid and repeated emergence of new types of antimicrobial resistance. Between 1988 and 1991, CDC documented a 50 percent increase in the proportion of resistant "gonococcal" isolates, most of them being resistant to penicillin or tetracycline (Wasserheit, 1995). As a result, CDC discouraged the use of the two drugs as first-line therapies against the organisms (Schwarcz et al., 1990). The origins of antibiotic-resistant gonococcus are unknown, but the organism has spread rapidly. In 1976, CDC found two cases of gonorrhea caused by organisms that produced an enzyme that destroyed penicillin. By the following year, health officials identified a strain called penicillinase-producing *N. gonorrhoeae* (PPNG) in 17 countries. In the United States most of the cases were in New York City, with three cases in 1977 involving resistance to penicillin, ampicillin, and spectinomycin. By 1981, treatment of gonorrhea had become far more complicated because of resistance to antibiotics (Garrett, 1994). The major impact of antibiotic resistance on gonorrhea is the cost of treatment. A nonresistant case of gonorrhea costs less than a dollar, but a resistant case may increase treatment anywhere between 12 and 15 times that amount (Morse, 1995).

Tuberculosis

Once thought to be conquered, tuberculosis (TB)—an airborne disease that is spread through the air when a person with active infection coughs, sneezes, or speaks, expelling contaminated droplets from the lungs—has re-emerged as a public health threat, with drug-resistant strains greatly complicating treatment. In 1947, when antibiotic therapy for TB was still considered a novel treatment and disease prevention technique, nearly 135,000 cases of the disease were reported in the United States. By 1985 the uses of streptomycin, rifampin, isoniazid, and other antibiotics, coupled with an aggressive public health effort to identify and treat TB cases, had brought the nation's caseload down to a little more than 22,000. By 1992, however, there were nearly 30,000 newly reported cases (OTA, 1993).

Well before the actual numbers of TB cases began to swell, the demographics of the disease shifted. Between 1961 and 1969 more than 80 percent of all active TB cases in the United States were among people over 62 years of age, and the majority of them were elderly individuals of European descent who had carried the *Mycobacterium tuberculosis* microbes in their bodies for decades, only falling ill as their aging immune systems failed to keep the bacteria in check. Most of these people were readily treated without hospitalization through basic long-term antibiotic therapy. Between 1975 and 1984 the numbers of active TB cases reported among the elderly declined sharply. By 1984, only 29 percent of TB patients were over 62 years of age. In the non-white population, less than one out of every five active TB cases that year involved someone over 62, and fully 20 percent were between the ages of 25 and 34. During that decade, white male cases dropped 41 percent, and white female cases fell 39 percent. While TB was declining across the board, its downturn among non-whites was slower; only 25 percent for males and 26 percent for females.

The warning signs were clear. Between 1980 and 1986 five different surveys documented a relationship between rising homelessness and the surge of TB in young adult populations, and by 1984 new resistant strains of drug-resistant TB were spreading among the urban indigent. By 1986, nearly half of all active TB cases reported in the United States were among non-whites, most of them African Americans. More specifically, TB now occurs disproportionately among individuals who lack stable housing, abuse alcohol or intravenous drugs, become incarcerated, are employed as migrant farm workers, and who, for various reasons, are exposed to people who do not adhere to treatment guidelines (OTA, 1993).

Geographically, the disease shifted from rural areas to scattered urban areas such as New York City and Miami. CDC noted the shift in 1986, which coincided with the first upward trend in TB cases reported in the United States since 1953. Agency officials believe that the impaired immune systems associated with HIV infection may be largely responsible for the increase in TB in New York City and Florida. However, other factors also can contribute to the spread of TB. A recent case in Minnesota prompted health officials there to theorize that heavy alcohol consumption may play a role in the weakening of the immune system, permitting initial infections to progress to active TB (Boodman, 1995).

In the mid-1980s, budget cuts in New York City forced a three-fold reduction in the number of TB clinics and disbanded public health clinics. During that same period, federal and state officials slashed TB control and surveillance budgets. For example, budget cuts eliminated New York City's surveillance system for multiple-drug resistant TB (MDR-TB) in 1986. Inadequate treatment and the lack of surveillance led to the increase in the number of MDR-TB cases. Frieden et al. (1995) analyzed TB surveillance data and discovered that drug resistance among patients who had never been treated increased from 10 percent in 1983 to 23 percent in 1991. Nearly 25 percent of patients with TB in New York City had multiple drug-resistant strains, and the proportion of new patients with MDR-TB had more than doubled from 1984 to 1991 (Freiden et al., 1995). From 1985 to 1992, public health officials documented outbreaks of MDR-TB in more than a dozen hospitals, homeless shelters, prisons, and other areas in the United States and Puerto Rico. Those cases are illustrated in table 3-1 (Garrett, 1994).

By the time politicians realized the scope of this re-emergence, TB, and especially MDR-TB, was draining already tight budgets and had become a public health crisis. When all the costs of the 1989-1994 MDR-TB epidemic were totaled, health officials had spent more than $1 billion to tackle the resistant bacteria (Garrett, 1994). Only after this crisis were federal dollars allocated and a modified surveillance system for MDR-TB reinstated (Berkelman et al., 1994). As a result of the revised surveillance system, along with directly observed therapy (in which health-care workers observe patients as they take each dose of medicine), New York City reported a 19 percent decline in all TB cases and a 44 percent decline in the MDR-TB cases from 1991-1992 to 1993-1994 (Freiden et al., 1995). Despite the recent successes, New York City has not controlled TB. The case rate there is still more than four times the national rate, and there are more patients in the city with MDR-TB than in the rest of the United States combined. However, New York City's experience shows that TB can be curtailed despite the prevalence of drug-resistant strains and immunosuppressed populations.

SURVEILLANCE OF ANTIBIOTIC-RESISTANT BACTERIA

Diseases are transmitted in the community, and some of those diseases are caused by antibiotic-resistant bacteria. How commonly that occurs is unknown. Almost all of the information about antibiotic-resistant diseases in the community comes from episodic reports, and it is unknown how many go unreported or unnoticed. Some exceptions are TB, syphilis, and gonorrhea, all of which are notifiable diseases, which means that CDC obtains and combines records from the states to provide national data on those infections. Public health officials at state health departments, CDC, and the Council of State and Territorial Epidemiologists recommend annual additions and deletions to the national notifiable disease list, which is published in CDC's Morbidity and Mortality Weekly Report. Generally, diseases are added to the list as new pathogens emerge and are deleted as their incidence declines. However, health officials in each state ultimately decide which diseases they will report on the nationally notifiable list. Table 3-2 shows a listing of nationally reportable diseases. Of the 50 diseases notifiable to CDC, 31 are bacterial and are therefore subject to antibiotic resistance.

Drug-resistant *S. pneumoniae* (DRSP) was added to the list of reportable diseases in 1995 as a result of a CDC-convened working group that identified methods for prevention and control of the bacterium. The working group, consisting of public health practitioners, clinical laboratory professionals, health-care providers, and representatives of professional societies, established DRSP, which is associated with many illnesses, as a nationally reportable condition. Currently, only a few states have made DRSP a reportable condition on a national level. If more states reported DRSP nationally, the system not only would provide better surveillance information but could serve as a model for surveillance of other antibiotic-resistant bacteria.

More surveillance information about the prevalence of drug-resistant microbes such as *S. pneumoniae*, for example, would enable physicians to prescribe antibiotics more effectively, thereby possibly reducing resistance, the added costs associated with treating an antibiotic-resistant disease, and in some cases death. Had the surveillance program for MDR-TB in New York City not been eliminated, perhaps more money

TABLE 3-1: MDR-TB Outbreaks in the United States and Puerto Rico, 1985-1992

Location	Drug resistance	Year(s)	Index case(s)	Secondary case(s)
Texas, California, Pennsylvania	INH, RIF, SM, PZA, EMB	1987	Male, diagnosed with TB in 1971; recalcitrant, in/ out of medications. Died in 1987.	9 family members and relatives
Mississippi, rural	INH, SM, PAS	1976	High school student	Fellow students and their families
Boston homeless shelters	INH, SM	1984, 1985	2 possible, both homeless men	Fellow sheltered homeless
Miami outpatient AIDS clinic or HIV ward	INH, RIF, EMB, ETH	1988-1991	1 patient	22 HIV patients
New York State Prison	INH, RIF, PZA, EMB, SM, KM, ETH	1990-1991	Prisoner	7 inmates and 1 prison guard
New York City Jail, Rikers Island	Various	1988-1992	Prisoners	Spread within jail; diagnosis rate of 500 per 100,000. Average daily census of jail is 20,000
New York City Jail	Various	1991	Prisoners	720 cases of MDR-TB diagnosed in prisoners
Waupun Jail, Wisconsin	NS	1993	Prisoners	22 prisoners
Nassau County Jail, New York	NS	1988-1990	Prisoners	45 prisoners
Lincoln Hospital, New York City	INH, RIF, EMB, SM	1991	Noncompliant AIDS patient	1 AIDS patient
7 New York City hospitals	INH, SM, RIF, EMB	1988-1991	Patients	More than 100 patients; 19 health-care workers, all but 6 of whom were HIV infected
San Juan, Puerto Rico, hospital	12 to INH, RIF, PZA, EMB	1989	Patient(s)	All 17 health-care providers on HIV ward infected
New York City hospital	NS	1989-1991	Patient(s)	23 patients, 21 of whom were HIV-infected; 12 health-care providers infected; no active cases
New York City hospital	INH, SM, RIF, EMB	1989-1990	Patient(s)	18 AIDS patients
Cook County Hospital, Chicago	NS	1991	Patient(s)	12 health-care providers infected; no active cases
Miami hospital	INH, RIF	1990-1991	Patient	36 patients, 35 of whom were HIV-infected
Miami hospital	INH, RIF	1987-1990	Patient(s)	29 patients, 13 health-care providers; no active cases

INH=isoniazid; RIF=rifampin; EMB=ethambutol; PZA=pyrazinamide; SM=streptomycin; PAS=para-amino-salicylic acid; ETH=ethionamide; KM=kanamycin; NS=not specified

SOURCE: Garrett, L. 1994.

TABLE 3-2: Infectious Diseases Classified as Notifiable at the National Level (United States, 1994)

AIDS	Hepatitis A	Rabies, animal
Amebiasis*	Hepatitis B	Rabies, human
Anthrax	Hepatitis, non-A, non-B	**Rheumatic fever***
Aseptic meningitis	Hepatitis, unspecified	**Rocky Mountain Spotted fever (Typhus fever, tickborne)**
Botulism	**Legionellosis**	Rubella
Brucellosis	**Leprosy (Hansen disease)**	**Salmonellosis***
Chancroid*	**Leptospirosis**	**Shigellosis**
Cholera	**Lyme disease**	**Syphilis**
Congenital rubella syndrome	**Lymphogranuloma venereum***	**Syphilis, congenital**
Diphtheria	Malaria	Tetanus
DRSP**	Measles	**Toxic shock syndrome**
Encephalitis	**Meningococcal infection**	Trichinosis
Escherichia coli O157:H7*	Mumps	**TB**
Gonorrhea	**Pertussis**	**Tularemia**
Granuloma inguinale	**Plague**	**Typhoid fever**
Haemophilus influenzae	Poliomyelitis	Varicella (chicken pox) +*
	Psittacosis	Yellow fever*

* Reports of these diseases are not printed weekly in Table I or Table II of the Morbidity and Mortality Weekly Report.

** Drug-resistant *Streptococcus pneumoniae* was added in 1995.

+ Although varicella is not officially a nationally notifiable disease, the Council of State and Territorial Epidemiologists encourages reporting cases of varicella to CDC.

SOURCE: Centers for Disease Control and Prevention. 1994. Morbidity and Mortality Weekly Report *43* (43):801.

NOTE: Boldface indicates bacterial diseases.

could have been saved in treatment, and more importantly, more deaths could have been prevented. However, since its reinstatement, the New York City TB surveillance system, along with directly observed therapy, as mentioned previously, has resulted in dramatic decreases in the number of TB and MDR-TB cases. Experiences in Washington State and Nevada in 1993 also demonstrate the usefulness of surveillance systems. Washington requires that hospitals report cases of illness caused by *E. coli* O157:H7 to the state health department. After health officials learned of a few cases, they determined that the bacteria were coming from fast-food hamburgers and recalled more than 250,000 hamburgers. This action ended the outbreak. Cases of *E. coli* infection derived from the same source had occurred earlier in Nevada, but without a surveillance system officials in that state were unaware of them until after the Washington health officials had detected their cases. Nevada's outbreak caused 58 cases of bloody diarrhea and acute kidney failure. None had been reported to the health department because physicians and laboratories were not testing for that particular pathogen.

CONCLUSIONS

Antibiotics have produced a great paradox. After their introduction into medical practice nearly 50 years ago, the drugs controlled many life-threatening diseases, reduced death and illness, and increased the life expectancy of Americans. Since then, the use of antibiotics, including inappropriate uses that have little benefit to the patients, has fostered antibiotic resistance and caused many antibiotics to lose their effectiveness against some bacterial diseases. As a result, some illnesses that were once easily treatable now pose problems for patients and physicians. One solution is the development of new drugs against antibiotic-resistant strains. However, strains resistant to the new antibiotics are likely to develop eventually. Therefore, a more long-term solution includes the more prudent use of antibiotics that are currently available.

Outbreaks of illnesses and diseases caused by antibiotic-resistant bacteria are increasing. How common these outbreaks are is unknown because of inadequate surveillance. Almost all of the information about antibiotic-resistant illnesses and diseases is episodic, and it is unknown how many go unreported or unnoticed. Surveillance is the essential element for health officials to identify, isolate, and control these outbreaks. The importance of a surveillance system was demonstrated in the *E. coli* outbreak in Washington State and Nevada in 1993. Health officials in Washington traced the outbreak's origin to undercooked hamburger from a fast-food chain. The finding led to the recall of more than 250,000 hamburgers and the end of the outbreak. In contrast, an outbreak from the same source had occurred earlier in Nevada and caused 58 cases of bloody diarrhea and acute kidney failure. Because of inadequate surveillance, the Nevada health officials did not identify their cases until after the Washington State cases occurred. Although these cases were not antibiotic-resistant, they serve as an example of how surveillance could track cases that are. In those instances, time is essential to prevent the spread of antibiotic-resistant illnesses that are generally harder to treat.

Although all persons are susceptible to illnesses related to antibiotic-resistant bacteria, some are more than others. The poor, people without adequate health care, the incarcerated, the homeless, military personnel, children in daycare facilities, the elderly, and the immunosuppressed are more susceptible to these illnesses than the general population. However, because most of the general public comes in contact with members of these vulnerable populations daily, the general public is at risk because the diseases or illnesses can spread from person to person. Because of the potential of widespread illnesses caused by resistant bacteria, better use of current antibiotics and more adequate surveillance systems would help control antibiotic resistance and reduce its effects on the general population.

Therefore, it is crucial that the scientific and medical communities, the pharmaceutical industry, and the general public cooperate to find solutions that will slow the pace of antibiotic resistance and lessen the impact of illness on public health.

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