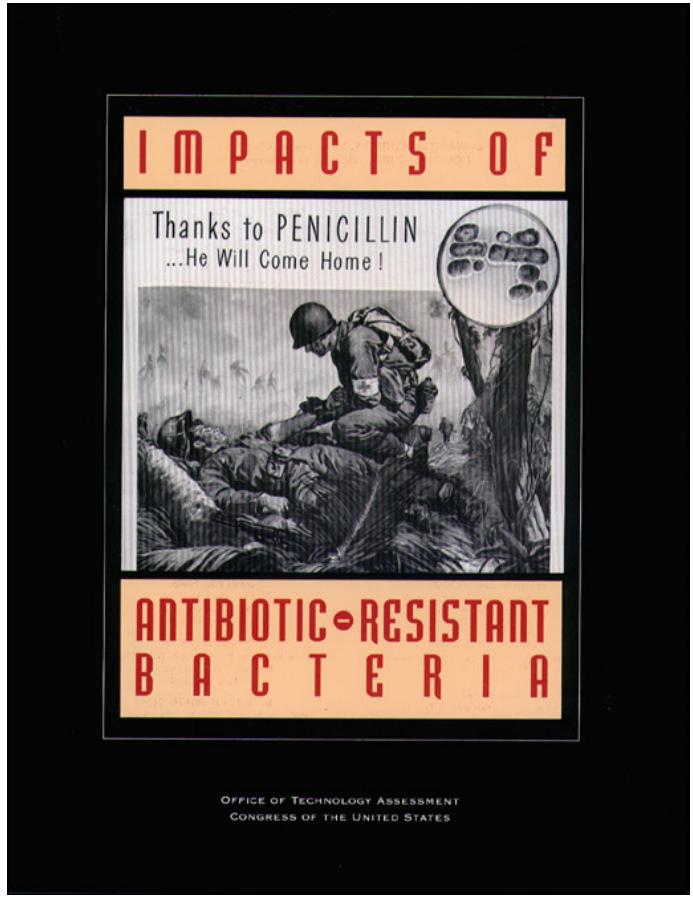
Impacts of Antibiotic-Resistant Bacteria

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Foreword

Penicillin, the first antibiotic, and the more than 100 other antibiotics now available to physicians are the primary weapons in mankind's battle against bacterial diseases. They revolutionized medicine, providing cures for formerly life-threatening diseases and preventing many previously inevitable deaths from infected wounds. They still do, but within a short time of each antibiotic's introduction into medicine, some bacteria became resistant to it, and the antibiotic lost its effectiveness against some diseases. Currently, few bacteria are resistant to all antibiotics, but many more are resistant to all but one or all but a few antibiotics, and the expectation is that resistant bacteria will continue to emerge and spread. The fear is that many bacteria will become resistant to all antibiotics, plunging humanity back into the conditions that existed in the pre-antibiotic age.

OTA's report discusses what is known about the emergence and spread of antibiotic-resistant bacteria and describes research and development aimed at controlling those organisms. It concludes that efforts are necessary both to preserve the effectiveness of currently available antibiotics and to develop new antibiotics. It discusses issues that arise in these activities, and it presents options for taking action.

This report was requested by the House Committee on Energy and Commerce in the 103d Congress (now the House Committee on Commerce). The Senate Committee on Labor and Human Resources in the same Congress endorsed the request for the study.

OTA was assisted in this study by an advisory panel of scientists and physicians from academia, industry, and state government chaired by Gail Cassell, Ph.D., of the University of Alabama at Birmingham. OTA gratefully acknowledges the contribution of each advisory panel member as well as that of many other experts who supplied information for the report and participated in reviews of the report as it was prepared. As with all OTA reports, the final responsibility for the content of the assessment rests with OTA.



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Summary, Conclusions, Issues and Options 1

SUMMARY

As more and more bacteria become resistant to the effects of antibiotics and as the flow of new antibiotics into medical practice slows, it is clear that the pronouncement of the Surgeon General of the United States nearly a quarter century ago that it was time to "close the book on infectious diseases" was premature.[1] Indeed, the popular press and some experts worry that we are headed toward an era of infectious diseases akin to the one that existed before antibiotics were introduced over a half-century ago.

This Office of Technology Assessment (OTA) report is a response to congressional requests (see box 1-1) for a description of the threat posed by antibiotic-resistant bacteria to our society. This report explores the biological bases for the development of bacterial resistance to antibiotics, describes new antibiotics that are in research and development, and outlines a number of strategies to control the proliferation of antibiotic-resistant bacteria.

Impacts of Antibiotic-Resistant Bacteria:

- ***Difficult-to-treat infections:*** Many strains of bacteria are resistant to one or more of the 100 antibiotics now in use. Physicians may have to try a number of different antibiotics until one proves effective.
- ***Untreatable infections***: Some strains of bacteria are resistant to *all* available antibiotics. Currently, infections caused by these bacteria are fairly uncommon, but they are rapidly increasing. Additionally, other bacteria are resistant to all but one antibiotic, and they are expected to become resistant to all antibiotics.
- ***Antibiotic use increases the spread of antibiotic-resistant bacteria***: Antibiotic use creates "selective pressure" that promotes the spread of resistant bacteria. Susceptible bacteria are killed or inhibited, and resistant bacteria survive and multiply. As bacteria become resistant to increasing numbers of antibiotics, the remaining effective antibiotics are used more often—increasing the selection pressure for bacteria to become resistant to them.

[1] Citations to the literature are not included in this summary. Complete citations are included in other chapters.

BOX 1-1: Origins of This OTA Study

In 1994, two Committees of Congress asked OTA to prepare a report that describes the incidence of infections with antibiotic-resistant bacteria in hospitals and in the community and any information about the costs of such infections. Moreover, the request asked how surveillance of antibiotic-resistant bacteria can be improved and for descriptions of the relationships between virulence and antibiotic resistance in bacteria, the state of the search for new antibiotics, and the success or lack of success in efforts to control the ongoing spread of antibiotic-resistant bacteria. In addition, OTA was asked to discuss issues that arise in attempts to control the impacts of antibiotic-resistant bacteria and to present options for actions by Congress and other organizations.

- ***Costs***: OTA estimates the in-hospital costs of hospital-acquired (nosocomial) infections caused by six common kinds of antibiotic-resistant bacteria to be a minimum of $1.3 billion. The estimate ignores the costs of infections caused by other kinds of antibiotic-resistant bacteria, costs of lost work days, and costs for post-hospital care. If these factors were considered, the total cost to society would be at least several billion dollars per year. Further, these costs can be expected to increase rapidly as the numbers of antibiotic-resistant bacteria increase.
- ***Antibiotic-resistant bacteria spread internationally***: Antibiotic-resistant bacteria are found all over the world and are spread among countries as people and goods are transported internationally.

Controlling Antibiotic-Resistant Bacteria

- ***Prolong the effectiveness of currently available antibiotics through three primary activities:***
  1) *Prudent use of antibiotics*: Studies indicate that many antibiotics are overused or used inappropriately. Physicians who prescribe antibiotics in the hospital or in their office practices often face difficult choices in deciding whether to prescribe an antibiotic and which one to prescribe. Surveillance systems to track the emergence and spread of disease-causing bacteria are essential. New technologies that quickly and accurately identify bacteria will improve use of antibiotics.
  2) *Vaccines*: Vaccines prevent infections and reduce the need for antibiotics. Effective vaccines against bacteria will reduce the use of antibiotics.
  3) *Infection control*: Effective infection control efforts range from simple procedures such as diligence in hand-washing to new materials for use in medical devices that impede the growth of bacteria.
- ***Develop new antibiotics***: New antibiotics are necessary to treat bacteria that are resistant to currently available antibiotics. Pharmaceutical companies are currently searching for new antibiotics by screening biological compounds for antibacterial activity and by use of new techniques to design molecules that are active against specific biochemical pathways in bacteria.

ORIGINS OF THE ANTIBIOTIC ERA

A century ago, physicians had few effective medicines to treat infectious diseases. Plenty of medicines existed, but most had no effect except to offer the relief associated with narcotics and alcohol. Physicians prescribed elixirs, nostrums, and potions for all sorts of illnesses. Systematic examination of their effectiveness, which began in the 1890s, showed that few had worth. With few effective treatments, the physician's role was limited to informing the patient and family about the expected course of the disease and keeping the patient comfortable, clean, and nourished

while waiting for the body's immune system to overcome the infection, if it could.

In 1928, the English microbiologist Alexander Fleming discovered that a common mold (Penicillium) produced a substance—penicillin—that killed bacteria. This became the foundation of a new era in treatment of infectious diseases. About a decade later, a British research and engineering team led by H.W. Florey developed methods for the large-scale production of penicillin. Penicillin became known as the "wonder drug," and diseases that were once life-threatening became manageable.

Over time, however, bacteria demonstrated their ability to "fight back." In 1945, shortly after penicillin's debut into hospitals, scientists isolated *Staphylococcus aureus* strains that were resistant to the drug, and by the 1950s, such strains were a common cause of disease in hospitals where penicillin had been heavily used. The semi-synthetic penicillin methicillin was temporarily effective against hospital strains of *Staph. aureus*, but only one year after methicillin's introduction in 1960, a study reported strains resistant to *it*. By 1991, more than 40 percent of *Staph. aureus* strains in some large hospitals were methicillin-resistant, and some of those strains were resistant to all antibiotics except vancomycin.

Vancomycin-resistant Enterococcus (VRE) are strains of Enterococcus resistant to the antibiotic vancomycin. Some strains of VRE are resistant to all Food and Drug Administration (FDA)-approved antibiotics.[2] In 1994, 15 percent of the enterococcus infections in intensive care units (ICUs) were resistant to vancomycin, as were almost 10 percent of the enterococcal strains acquired outside the ICUs.

Today, antibiotics remain effective against most bacterial diseases, but some antibiotics are no longer effective against infectious diseases that they defeated only a few years ago. Moreover, the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE and the expectation that other bacteria will develop resistance to all or almost all antibiotics warn that we may be entering a post-antibiotic era.

SURVEY OF ANTIBIOTIC RESISTANCE

The Microbial Battlefield

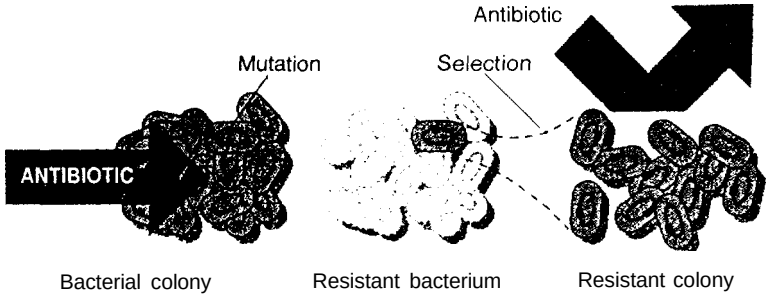
The ongoing survival contest between microorganisms and antibiotics dates back millions of years. Bacteria live in the soil and other places where they compete with other bacteria and microorganisms for nutrients. Over time, some microorganisms, such as the Penicillium mold, have evolved the biochemical machinery to produce antibiotics, such as penicillin, that inhibit growth of or kill bacteria. This eliminates competitors for nutrients.

"Antibiotic-resistant bacteria" are strains of bacteria that were once susceptible to an antibiotic but have since acquired resistance after the introduction of antibiotics into medical practice. Antibiotic resistance operates through one of four general mechanisms. The resistant bacterium: 1) does not absorb the antibiotic, or 2) expels it, or 3) degrades it, or 4) has altered the usual molecular target for the antibiotic so that the drug has no effect.

Resistance results from mutations that arise spontaneously in bacteria. Mutation is a rare event—occurring once in a few million or a few hundred million bacteria, for instance—but the probability of a mutation occurring during an infection is the product of mutation and the number of bacteria, and millions of bacteria can be present in an infection. If a mutation for resistance to an antibiotic does occur, and if the person is being treated with that antibiotic, the antibiotic will kill off or inhibit the non-resistant or "susceptible" bacteria (see figure 1-1), leaving the antibiotic-resistant bacteria to multiply and flourish. This is the process of "selection." More

[2] A drug now in the final stage of clinical trials may work against some strains of VRE, and it is available under an FDA emergency-use program, upon request to the manufacturer (Rhone-Poulenc Rorer, 1995).

FIGURE 1-1: Mutation and Selection of a Colony of Antibiotic-Resistant Bacteria



NOTE: A mutation that makes a bacterium resistant to an antibiotic can arise spontaneously when the antibiotic is applied: only the resistant bacterium can grow and divide.

SOURCE: *Time,* September 12, 1994, p. 67.

frequent use of antibiotics creates more pressure for the selection of antibiotic-resistant bacteria. Many antibiotic-resistant bacteria can transfer to other bacteria the genetic material that makes them resistant to antibiotics, contributing greatly to the spread of antibiotic-resistant bacteria.

Because the use of antibiotics selects for the emergence and spread of antibiotic-resistant bacteria, it is important to use antibiotics carefully. **According to some estimates, as much as 50 percent of antibiotic use is inappropriate because the uses do not benefit the patient. These uses do increase selection pressure for the emergence and spread of antibiotic-resistant bacteria.** Physicians often face difficult choices in deciding whether to prescribe an antibiotic. Understanding how some of those decisions are made is essential for understanding the problem of inappropriate use of antibiotics.

▮ Antibiotic Use in Hospitals

At any given time, about 25 to 35 percent of hospital patients are under antibiotic treatment for active infections or to prevent potential infections. The large volume of antibiotic use exerts enormous selective pressure for the emergence and spread of antibiotic-resistant bacteria. Therefore, untreatable bacteria, such as some strains of VRE, and hard-to-treat bacteria are much more common in hospitals than in the community at large.

▮ Antibiotic Use in Physicians' Office Practice

A parent who brings in a child with one of the 24.5 million middle ear infections (otitis media) that occur annually hopes for an immediate diagnosis and treatment. The child is cranky; the parent is probably missing work to take care of the child; and the parent may know that recurrent ear infections can result in impaired speech, language and cognitive development. By age three, about three-fourths of all American children will have had at least one episode of otitis media, and more than one-third will have had recurrent infections.

A physician usually refrains from puncturing the ear drum to obtain a sample of material for laboratory identification. Waiting for the earache to clear up on its own may leave the child in unnecessary pain, increase the number of sleepless nights for the child and family, and potentially contribute to more serious illness. Consequently, physicians often prescribe antibiotics, though studies show that only one-third to one-half of otitis media cases benefit from antibiotics. Many otitis media cases that do not respond to antibiotics are caused by viruses, against which no antibiotic has any effect. Studies also show that many bacterial infections will go away without antibiotic treatment, although use of antibiotics may shorten the course of the illness.

Faced with the uncertainties of diagnosis and the certainty that at least some of their patients will benefit from antibiotics, most physicians will prescribe an antibiotic, generally amoxicillin, because it is usually effective against all three of the common bacterial causes of otitis media. Even so, amoxicillin will be ineffective against 10 to 15 percent of infections caused by the three common bacterial agents of otitis media because the bacteria will be resistant. Another antibiotic may have to be prescribed in those cases.

Experience of treatment failures with amoxicillin may encourage the physician to routinely prescribe antibiotics other than amoxicillin. Antibiotic prescription patterns are also influenced by patient expectation or demand (see box 3-1 in chapter 3 for misperceptions about antibiotic use) and promotion by pharmaceutical companies.

Antibiotic Resistance in the Community

Everyone is at risk for infections caused by antibiotic-resistant bacteria, but some populations are at particularly high risk. Those communities range from the poor, who often live in crowded conditions with less than optimal hygiene and medical care, to middle-class children in daycare centers, who are at high risk for otitis media and other infectious diseases. Other populations at higher risk are people in institutions such as hospitals, nursing homes, prisons and military installations. People with diseases or conditions that suppress the immune system are also at increased risk. However, once antibiotic-resistant bacteria emerge in these populations, they can be spread widely to other groups.

Factors in the Emergence of Antibiotic-Resistant Bacteria

Some of the bacteria acquired in the community are antibiotic-resistant and have been carried into the community by people returning from hospitals where antibiotic-resistant bacteria are more common. Some arrive by other means. Modern transportation has fostered global accessibility and allows humans and their microbes to travel more quickly than ever before. For example, epidemiologists have tracked the spread of a multiple-resistant strain of *Streptococcus pneumoniae* from Spain to Iceland. Other factors that contribute to the emergence and spread of antibiotic-resistant bacteria, as well as the spread of other bacteria in the community are improper food preparation practices both in homes and commercial establishments, inadequate water treatment and inspection, and poor sanitation and hygiene.

Prevalence of Antibiotic-Resistant Bacterial Diseases in the Community

No one knows how common antibiotic-resistant bacteria are in the community. The United States has no surveillance system to track antibiotic-resistant bacteria over wide areas, and our knowledge of community patterns is restricted to a few studies in specific geographic areas and to information about antibiotic resistance in gonorrhea and tuberculosis. Both are “notifiable diseases,” and cases of these diseases are to be reported to the Centers for Disease Control and Prevention (CDC). Even so, information about the antibiotic susceptibility or resistance of those bacteria is often not obtained or reported.

Gonorrhea

Penicillin-resistant strains of *Neisseria gonorrhoeae* are now found in at least 17 countries. Between 1988 and 1991, CDC documented a 50 percent increase in the proportion of penicillin- or tetracycline-resistant *N. gonorrhoeae*. This finding led CDC to discourage the use of penicillin or tetracycline as first-line treatment for the disease. Gonorrhea is an example of widespread resistance forcing the use of newer, more expensive antibiotics as primary treatment. In welcome contrast, *Treponema pallidum*, the cause of syphilis, remains universally susceptible to penicillin.

Tuberculosis

Public health measures and the use of antibiotics reduced the number of tuberculosis (TB) cases

from 135,000 in 1947 to 22,000 in 1985 and fueled the expectation that the disease would be conquered. By 1992, however, the number of cases had resurged to 30,000.

Drug-resistant strains of TB present a major challenge to health officials. In 1991, in New York City, 14 percent of all newly diagnosed TB cases were resistant to one or more antibiotics used for primary treatment, and 60 percent of the relapse cases in the first 12 weeks of the year were multiply drug resistant (MDR). These strains spread from impoverished homeless populations of New York City to their health care providers, jail guards, fellow patients inside hospitals, and other parts of the country. Table 1-1 illustrates the MDR-TB outbreaks in the United States and Puerto Rico from 1985 to 1992.

Antibiotic Use in Animal Husbandry

Probably no other issue about antibiotic-resistant bacteria elicits more emotion than questions about the impact of the use of antibiotics in animal husbandry on the appearance of antibiotic-resistant bacteria in humans (see chapter 7).

About half, by weight, of the antibiotics used in the United States are used in the production of food animals, such as swine, cattle, and poultry, and the most used antibiotics are "old" ones, penicillin and the tetracyclines. Almost 90 percent of the agricultural use is for prophylaxis or growth promotion, rather than for treatment of sick animals.

Long-term use of antibiotics such as penicillin and tetracyclines decreases the time necessary to raise an animal to marketable weight or reduces the amount of feed necessary to reach such weights. Perhaps because those uses are equated only with economic gain, the strongest criticisms have usually been addressed at such long-term uses.

There is no question that agricultural uses of antibiotics select for antibiotic-resistant bacteria just as do medical uses. For instance, some antibiotic-resistant Salmonella cases have been traced back to meat from animals fed antibiotics. Questions arise about the quantitative public health importance of antibiotic-resistant bacteria from agriculture. No differences in the prevalence of antibiotic-resistant bacteria were found between groups of people who ate meat and groups who did not eat meat. Indeed, there was a slightly increased frequency of multiply resistant bacteria in the vegetarians. These results are consistent with the conclusion that meat is not the only source of antibiotic-resistant bacteria, but they do not show that meat is unimportant nor do they pinpoint the other sources of antibiotic-resistant bacteria in the diet.

Over the last two decades, the FDA, the National Academy of Sciences, OTA, and official boards and committees overseas have examined the evidence for the contribution that agricultural uses of antibiotics make to human diseases or to the prevalence of antibiotic-resistant bacteria. None was able to pinpoint data that show the extent of the problem, and all have pointed to the great difficulties in studying this issue.

COSTS OF ANTIBIOTIC-RESISTANT BACTERIAL DISEASES

Because of the costs involved in controlling and monitoring the spread of antibiotic-resistant bacteria, it would be useful to know how much would be saved by reducing the impacts of antibiotic-resistant bacteria. Calculation of the costs imposed by antibiotic-resistant bacteria can include such factors as the direct cost of time in a hospital, the costs of extra physicians' visits when antibiotics are ineffective, the extra hospitalizations due to community-acquired resistant infections, and the costs of newer antibiotics to replace antibiotics to which bacteria have become resistant. Other costs include lost work days and deaths, if they occur. Only one such study has been published, and it included the estimate that the cost of antibiotic-resistant bacteria nationwide was between $100 million and $30 billion annually, with different values attached to the cost of a life accounting for most of the wide range of the estimate. A medical

TABLE 1-1: 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.

society subsequently estimated the costs of such diseases at $4 billion.

In this report, OTA calculates the direct hospital costs from five classes of nosocomial infections associated with only six different strains of antibiotic-resistant bacteria and concluded that the minimum nationwide hospital costs of those infections was $1.3 billion in 1992 dollars. Adding other infections associated with other bacteria and other costs in addition to direct hospital costs would increase the total to several billion dollars. This number can be expected to increase as the numbers of antibiotic-resistant bacteria increase.

REDUCING THE IMPACTS OF ANTIBIOTIC-RESISTANT BACTERIA

The impacts of antibiotic-resistant bacteria can be reduced by preserving the effectiveness of current antibiotics through infection control, vaccination and prudent use of antibiotics, and by developing new antibiotics specifically to treat infections caused by antibiotic-resistant bacteria.

Preserving the Effectiveness of Current Antibiotics

Reducing infection rates, which will reduce the demands for antibiotics, will reduce the pressures for selection of antibiotic-resistant bacteria.

Surveillance

Surveillance systems are necessary to track patterns of antibiotic resistance. At the local level, physicians can use the information to choose appropriate antibiotics. At the national level, pharmaceutical companies can use the information to plan new drug development.

Many hospitals have surveillance systems to track the spread of disease-causing organisms, including antibiotic-resistant bacteria, and to provide information to physicians about the use and effectiveness of antibiotics. These systems have saved hospitals money; for example, a system in the LDS Hospital in Salt Lake City, Utah, monitored the use of prophylactic antibiotics before surgery. This system reduced unnecessary antibiotic use and saved $42 per patient, resulting in a projected cost savings to the hospital of $89,000 per year.

At the state level, the New Jersey Department of Health collects data about antibiotic-resistant bacteria from microbiology laboratories in each of the 95 acute care general hospitals licensed by the Department. Since its inception in 1991, all New Jersey hospitals have submitted monthly reports to the Department of Health, which collects and analyzes the data and makes it available to all participating hospitals and to the public. The surveillance system has been used to study many questions about antibiotic-resistant bacteria including: patient risk factors for VRE bacteremia, the role of antibiotic usage in VRE bacteremia, the effectiveness of infection control practices in preventing nosocomial transmission of VRE, and VRE susceptibility to the experimental drug quinupristin/dalfopristin. The system's operation requires about a day's work by one person each month in the State Department of Health.

SCOPE, Surveillance and Control of Pathogens of Epidemiological Importance, is a national effort established by the University of Iowa and Lederle Laboratories (now Wyeth-Ayrst Lederle Laboratories) in 1995. The program expects to collect reports of all nosocomial bloodstream infections in 48 hospitals nationwide as well as samples of the organisms isolated from the infected patients. The reports will provide information about the spread of antibiotic-resistant bacteria in the hospitals.

There are also other industry-funded surveillance systems. A number of academic and commercial laboratories conduct surveillance under contract to pharmaceutical companies, but they are not necessarily designed to obtain information most useful for public health purposes.

The CDC-run National Nosocomial Infection Surveillance (NNIS) is the single nationwide surveillance system that produces information about antibiotic-resistant bacteria. While it is limited to reports on nosocomial infections from about 200 hospitals, it is the source for most of the data in this report about MRSA, VRE, and other drug-

resistant bacterial infections. NNIS publishes results infrequently and at long intervals after the data are collected. NNIS, in whatever form it continues, should be urged to publish in a timely fashion so that data can be used more efficiently.

CDC is in the early stages of establishing nationwide surveillance of drug-resistant *S. pneumoniae* (DRSP), which will cover infections whether or not they occur in a hospital. Successful establishment and operation of that system could provide a model for surveillance of all antibiotic-resistant bacteria, but the full system would require additional funding. As an early step in setting up the DRSP system, and at CDC's request, the Council of State and Territorial Epidemiologists has recommended DRSP for inclusion on the list of notifiable diseases, and four states now report it. The CDC initiated DRSP in 20 laboratories in New Jersey in April 1995, and if funds are available, CDC expects that most of the nearly 2,000 hospital and commercial laboratories that now have computerized record keeping will be on the system by 1998. As laboratories add computer capabilities, the CDC will encourage them to enlist in the system, expecting that all of the nearly 5,000 laboratories in the country will eventually participate. If the DRSP system works, CDC envisions expanding it to include other antibiotic-resistant bacteria.

WHONET, an established surveillance project, is a computer-based system that is sponsored by the World Health Organization. It tracks the resistance patterns of bacteria in clinical microbiology laboratories in hospitals worldwide and provides the participating hospitals with methods to follow the spread of antibiotic-resistant bacteria and to examine the efficacy of local infection control procedures. WHONET was established by two people, and it is maintained single-handedly by Dr. Thomas O'Brien of the Brigham and Women's Hospital, Boston, MA.

Even with its limited resources, WHONET has about 100 participating hospitals, and some of those hospitals report information from large areas, up to the size of countries. It is a primary source of data about antibiotic-resistant bacteria around the world, and it provides a method to track the flow of bacteria from country to country. It also provides scientists in the participating hospitals a powerful tool to analyze the spread of antibiotic-resistant bacteria in their own hospitals.

Vaccines

Vaccines now protect millions of people from bacterial and viral diseases, and as shown in figure 1-2, successful vaccines can have a rapid, profound effect on bacterial disease rates. Vaccines that are successful against pathogenic bacteria will protect against both antibiotic-sensitive and antibiotic-resistant strains and reduce the need for antibiotics and the selection pressure for the emergence of resistance. While the rate of introduction of new vaccines has been slow in years past, new developments in molecular biology research may increase the rate in the near future.

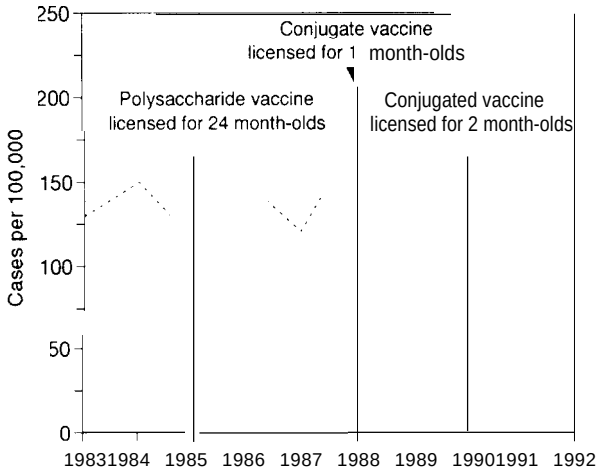
The policies surrounding vaccine development in the United States are not a focus of this OTA report, but the Federal National Vaccine Program is often described as faltering and research as underfunded.

Infection Control

Infection control measures are a crucial element in preserving the effectiveness of current antibiotics. A 1976 CDC study showed that hospitals with intensive infection control and surveillance programs could reduce the approximately two million infections acquired in hospitals per year by 32 percent. The report identified handwashing, improved hygiene, and patient isolation as successful infection control efforts.

Despite whatever infection control methods were put in place, the number of bloodstream infections increased by 70 percent in large teaching hospitals and 279 percent in small non-teaching hospitals during the 1980s. These increases, in part, reflect the increased life-saving capacity of modern medicine that includes increased surgery rates with attendant catheterizations and other invasive procedures, organ and tissue transplants that require immunosuppression to pre-

FIGURE 1-2: Invasive Hib Disease in Los Angeles County Children Aged 6 to 12 Months



SOURCE: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases. 1994. *Annual Report,* p.1.

vent rejection of the transplant, and more aggressive treatment of cancer and other diseases with chemicals and radiation that also cause immunosuppression. All of these procedures increase the risk of infection.

Even simple infection control measures may be difficult to institute in practice. In one study, nurses believed they adhered to hand washing practices nearly 90 percent of the time, when the actual observed rate was between 22 and 29 percent. However, professional organizations, such as the Association for Professionals in Infection Control and Epidemiology (APIC) and the Society of Healthcare Epidemiology of America (SHEA), provide forums for hospital staff and other health care professionals to study and understand the transmission of infections and methods to control it. They support independent organizations for the certification of individuals as being qualified to work in infection control on the basis of education and knowledge.

Materials and Device Design to Reduce Infections

Many of the several hundred thousand annual nosocomial infections associated with the use of medical devices, such as catheters, endotracheal tubes and mechanical ventilators, can be prevented. The use of biocompatible dialysis membranes for kidney patients has reduced infections by 50 percent; synthetic suture materials such as Dacron and Nylon had lower infection rates than natural sutures; new designs in catheters prevent microorganisms on the skin from penetrating the body; and coating or impregnating catheters with antibacterial agents has also reduced rates of infections in some studies.

New Antibiotic Delivery Systems

Direct application of antibiotics to infected areas or areas likely to be infected can produce local concentrations of antibiotics sufficiently high to overcome some resistant bacteria without producing high concentrations of circulating antibiotics. Researchers at the Walter Reed Army Institute of Research have developed microsphere of biodegradable polymers and antibiotics that can be dusted directly into wounds, and other researchers have used an antibiotic-impregnated polymer to cement bone fractures and prostheses in place, and a new material, which can also be impregnated with antibiotics, can be used as cement and as replacement for destroyed bone.

Possible Alternatives to Antibiotics

Before antibiotics were available, physicians used other therapies against bacterial infections. Serum therapy consists of using blood (or blood fractions) from animals that have survived a particular bacterial infection to treat humans infected with the same organism. This treatment is complicated by the adverse side-effects that accompany injection of foreign blood proteins, but it has been shown effective in treating infections caused by *Escherichia coli O* 157:H7 in laboratory animals. That bacterium produces a toxin that can be inactivated by serum treatment; antibiotics have no positive effect on the infections, and may make them worse by liberating the toxin.

"Phage" or "bacteriophage" are viruses that infect and kill bacteria. Physicians used them to treat human infections in the years between the World Wars, and they were the research project of the physician in *Arrowsmith.* Some scientists believe study of their possible use in a post-antibiotic era may be justified.

While both phage and serum therapy are sometimes suggested as alternatives to antibiotics, the rapid disappearance of both therapies after the introduction of antibiotics points to their less-than-successful past. These old therapies are not likely to receive serious consideration unless effective antibiotics disappear.

Optimizing Antibiotic Use

A comparison of prescription records to verified causes of disease shows that antibiotics are often prescribed for viral infections, for which they have no value, and for self-limited infections that would have cleared up whether or not an antibiotic had been prescribed. Of course, the prescriptions are often, necessarily, written in advance or in the absence of the laboratory testing required to verify causes. While these cases offer evidence of inappropriate use of antibiotics, many of them are, at least partially, understandable. **Clearly inappropriate, however, is the administration of prophylactic antibiotics at times greater than two hours before or after surgery; antibiotics administered at these times are ineffective for preventing surgical wound infections.** Reducing inappropriate uses should retard the development of antibiotic resistance, and over the years, academicians and scientists have urged better education of physicians about antibiotic use and resistance.

A new educational initiative being planned by a number of pharmaceutical companies, the American Society for Microbiology, and CDC will produce educational materials encouraging more appropriate use of antibiotics. Other organizations are making similar efforts. Evaluation of the success of those efforts could pinpoint the items in the educational package that make the most difference. OTA's 1994 report *Identifying Health Technologies That Work* describes the features of successful programs designed to influence physician behavior.

Past educational efforts have had limited effect, partially because not all cases of "overuse" are as clearly defined as the case of inappropriately prescribing prophylactic antibiotics. For example, different interpretations are possible of the wisdom of giving a prophylactic dose of antibiotics to the President after his exposure to a low risk of contracting an infection (see box 1-2). Another example is one type of ear infection (otitis media with effusion). The Agency for Health Care Policy and Research recently wrote a guideline to clarify treatments for otitis media (not necessarily to promote prudent use of antibiotics) and concluded that:

> Meta-analysis for Guideline development showed a 14 percent increase in the probability that otitis media with effusion would resolve when antibiotic therapy was given versus no treatment....When this small improvement in resolution of otitis media with effusion is weighed against the side effects and cost of antibiotic therapy, antibiotic therapy may not be preferable to observation in management of otitis media with effusion in the otherwise healthy young child....

A physician who elected not to prescribe an antibiotic, foregoing the 14 percent increased probability that the condition "would resolve," might be liable for legal action. Such potential liability might encourage physicians to prescribe antibiotics even when they may not be indicated. The above guidelines do not instruct physicians to consider the spread of antibiotic resistance in the decision to prescribe antibiotics, only the cost and risk vs. benefit of the antibiotic to the patient.

Some hospitals control drug use by establishing formularies, listings of approved drugs for various medical indications. Some Denver, Colorado, area hospitals combined their formularies with a computerized antibiotic order form that requires physicians to enter the suspected cause of infection. The system saved the hospitals money, and allowed officials there to change the formularies when susceptibility tests revealed a new pattern of antibiotic resistance.

BOX 1-2: The President's Doctor's Dilemma

On June 13, 1995, President Clinton took antibiotics to prevent a possible case of meningitis after shaking hands with a college student who was diagnosed with the disease (*Washington Post*, June 14, 1995, page A6).

Meningitis is often caused by *Hemophilius influenzae* type b (Hib), *Neisseria meningitidis*, or *Streprococcus pneumoniae*. A standard textbook (Mandell, Douglas and Bennett's *Principles and Practices of Infectious Disease*, 4th Edition, pages 856–857) describes considerations for deciding when prophylactic antibiotics are necessary after contact with a patient with meningitis. For meningitis caused by Hib, the textbook states that prophylaxis is indicated for household contacts, and possible for day care contacts, "...in day care centers that resemble households where children have prolonged contact." For meningitis caused by *N. meningitidis*, the textbook states that "Chemoprophylaxis is recommended for close contacts of the index case, defined as household contacts or close contacts in a closed community such as a military barracks or boarding school, and medical personnel performing mouth-to-mouth resuscitation." For meningitis caused by *S. pneumoniae*, the textbook states that in one outbreak in a day care center, chemoprophylaxis "...did not prevent new acquisition of this organism by three children and one family member. Further studies are needed before chemoprophylaxis is recommended for contacts of patients...."

Prescribing a dose of antibiotics for the President after he shook hands with someone with meningitis is an example of individual vs. public health considerations in the use of antibiotics. Shaking hands is a pretty minor contact; far less intense than those for which the textbook recommended prophylaxis. However, even the insignificant chance that the President was infected was considered worth one dose of antibiotics. This illustrates a dilemma about appropriate antibiotic use. The President had the benefit of the antibiotic preventing a very small risk. The use of the antibiotic might increase the spread of antibiotic-resistant bacteria. Millions of such cases, justified on similar individual bases, would add together to increase the risk of spread of antibiotic resistance.

Managed care plans are beginning to employ Pharmacy Benefit Managers (PBMs) to monitor pharmacy use. PBMs analyze pharmacy use data to control costs and they may be helpful in setting guidelines for appropriate antibiotic use.

The LDS hospital in Salt Lake City, Utah, developed a computerized antibiotic monitoring system, which is part of a larger computerized patient record system that automatically collects surveillance data and generates profiles of antibiotic resistance in the hospital's bacteria. Clinicians enter the results of susceptibility tests into the computer which checks to be certain that any prescribed antibiotic will work and generates an alert when an antibiotic is inappropriate. Another part of the hospital's system is a computerized antibiotic consultant, which uses surveillance data along with information about the site of infection and patient allergies to determine the best choice of empiric antibiotic therapy. As judged by a panel of infectious disease experts, this computer consultant "chose" the appropriate antibiotic 94 percent of the time, as compared to a 77-percent rate for the physicians. These systems require up-front costs with no guarantee that the costs will be recouped. Thus, convincing hospital administrators to invest in such a system in financially strapped times appears difficult, despite the advantages such a system could bring to a hospital.

Diagnostic Technologies

Sore throats, as well as ear aches, are often mentioned in connection with the overuse of antibiotics. When a physician sees a patient with a sore throat, the physician asks about the patient's symptoms, examines the patient's throat, notes the inflammation, and may swab the throat to pick up any organisms that are there. If the physician is like more than 40 percent of all primary

care physicians, he will begin antibiotic treatment without any more information. This is partly because of the time necessary for a laboratory to identify the bacteria associated with an illness.

Chapter 6 describes methods currently used to identify bacteria and to determine their antibiotic susceptibility. Methods to determine susceptibility rely on putting the bacteria into culture media, where the bacteria will grow, and also putting them into culture media with known concentrations of antibiotics. Laboratory personnel then determine which antibiotics and which concentrations of antibiotics inhibit the growth of or kill the bacteria.

More rapid methods for making diagnosis might improve the physician's decisions about prescribing antibiotics, but only if the results have high reliability. "Quick strep" tests for sore throats produce results in 20 minutes. If the test result is positive, 95 percent of the time the result is accurate and strep is present. If the test does not indicate strep, there's a 20–30 percent chance that strep was present, but the test missed it. Guidelines recommend a follow-up culture for all negative "quick strep" tests. The result is that the "quick strep" test probably affects practice only marginally. All patients with a positive "quick strep" test will surely get an antibiotic, and many with a negative test will get antibiotics as well (at least until the results of a standard culture assay are available). This result differs little from what would likely happen in the absence of the test. The test provides an advance in the right direction, but further advances are necessary.

A strep test that employs DNA methods reportedly produces results sufficiently accurate so that they do not have to be verified by standard tests. However, the test is so involved that its use will probably be restricted to large practices or hospitals. Moreover, it produces results in a few hours, not in a few minutes. Even if this test proves to be as good as it appears and it is adopted where there are large numbers of patients, it will not produce results during the course of an office visit. The physician may elect to give the patient a prescription with instructions to call the office in a few hours to learn the test results before the prescription is filled (or discarded). Of course, the patient might have the prescription filled regardless and save it for another time. The impact of any test will depend a great deal on the interactions between physician and patient until the results are so rapid that they are complete before the patient leaves the office.

Faster tests may have a marked impact in the diagnosis of tuberculosis so that patients can be treated before they pass the infectious disease to others. Isolation of the slowly growing Mycobacterium causing tuberculosis requires three to eight weeks, and susceptibility testing by traditional methods can add 20 days to six weeks. New diagnostic tests based on identifying mycobacterial DNA are being developed to allow physicians to identify Mycobacteria in the sputum of patients within a few hours to a few days.

New diagnostic technologies raise some new issues. For instance, the DNA test for tuberculosis might be so sensitive that it can detect the DNA of Mycobacteria already killed or inhibited by previous treatment. To act entirely on the test result might result in treatments that are unnecessary.

Tests which directly measure the presence of an antibiotic-resistance gene in bacteria also bring a new set of considerations. A gene for resistance that is detectable by the new tests might not be "expressed," and its detection might not accurately predict whether the bacteria will be resistant or susceptible. Or a resistance gene may have undergone a mutation that does not affect its function, but alters it so that a genetic test might not register the presence of the antibiotic-resistant gene. All these issues are anticipated in designing genetic tests and bringing them to clinical practice.

Practice Guidelines

Practice guidelines are medical protocols that are intended to assist practitioners in making clinical decisions. For example, the Agency for Health Care Policy and Research (AHCPR), a federal agency empowered to establish practice guide-

lines, encourages health care providers to adopt its guidelines to improve patient care, patient outcomes, and quality of life. Practice guidelines that are written to balance patient benefits and public health effects and that provide specific direction about antibiotic use might reduce overuse. Nationwide data cannot capture the localized nature of antibiotic-resistant bacteria, but an online computer system linking health care practitioners in a geographic area could provide that information. Such a system would allow health care practitioners to consult with specialists in determining the best way to comply with the practice guidelines and would also allow health care practitioners to enter the specifics of their cases.

Designing New Antibiotics

In the arms race with resistant bacteria, drug manufacturers have research programs to isolate or synthesize new antibiotics or to develop derivatives of old ones that have greater antibacterial activity, fewer side effects, or that can be administered orally rather than requiring injections. Researchers are continuing to search through samples of soils and other materials rich in molds and bacteria, which have yielded many of the existing antibiotics, and they have widened the search to include carbohydrates, proteins, and steroids from many biological sources. Companies are investigating the use of modern chemical techniques to design new molecules for specific purposes. While the payoff from any line of research remains uncertain, many small, new companies as well as the older, established pharmaceutical companies are sufficiently confident of producing useful products that they are investing in antibiotic research (see chapter 5). Table 1-2 lists some currently used and in-development antibiotics.

New antibiotics can be divided between those that are improvements on already-existing drugs, which depend on known mechanisms of action, and those drugs that have new mechanisms of action. None of the nine antibiotics approved by FDA in 1992 and 1993 had a new mechanism of action, and no antibiotic was approved in 1994.

Antibiotics that depend on "old" mechanisms of action can be very useful (and profitable). For instance, cefaclor, a third-generation cephalosporin, accounted for 15 percent of a major pharmaceutical company's sales when its patent expired in 1992. It remains a clinically useful drug, and the company expects to retain a major part of the market for cephalosporins even after the expiration of patent protection. In general, however, antibiotics with new mechanisms of action might be expected to be more successful as therapies against certain antibiotic-resistant bacteria because no similar antibiotics exerted pressure for the selection of resistance to them in the past. Many of the substances currently being examined as potential antibiotics have novel mechanisms of action, and some may not foster the development of resistance (see chapter 5).

The isolation or synthesis of a chemical with antibiotic activity starts a long process of evaluation in the microbiology lab, laboratory animals, and ultimately, in humans. At the end of those tests, FDA reviews the results and considers approving it as a new drug (see figure 1-3). The entire process between discovery and final approval takes years; frequently a potential drug fails a critical test—for instance, it is found to have toxic side effects—and is discarded. The risks of toxicity may be re-evaluated against the benefits of an antibiotic, however, if the antibiotic proves useful against a disease with few or no other treatments.

Pharmaceutical firms are largely responsible for antibiotic research and development, but the federal government supports a small research program aimed at antibiotic-resistant bacteria at the National Institute of Allergy and Infectious Diseases. In 1994, the institute spent about $13 million on that program, and about the same amount in 1995.

Antibiotic Resistance and Markets

Antibiotic resistance both limits and creates new markets. Although drugs may lose their efficacy and market life because of resistance, their slide

Action	Family/Class	Example(s)	Source	Status
Antibiotics that inhibit cell wall synthesis	Beta-lactams			
	Natural penicillins	Penicillin G	*Penicillin notatum*	Used since 1940s
	Semi-synthetic penicillins	Methicillin	Semi-synthetic penicillin derivatives	In use since 1960s; among the most widely prescribed antimicrobials
		Piperacillin		
	Cephalosporins	Cephalexin	*C. acremonium*	Widely used class of antibiotics
	Carbapenems	Imipenem	Derived from thienamycin, a compound produced by *Streptomyces cattleya*	In use; wide spectrum (active against many species of bacteria including cephalosporin-resistant Enterobacteriaceae)
	Monobactams	Aztreonam	Derived from a compound produced by *Chromobacterium violaceum*	In use; tolerated by patients with penicillin allergies; spectrum limited to aerobic gram-negative bacteria
	Penicillinase inhibitors	Clavulanate potassium (used clinically with amoxicillin or ticarcillin)	*Streptomyces clavuligerius*	Used since 1970s; clavulanate combinations used for wide range of disorders
		Subtraction (used with ampicillin)	Semi-synthetic penicillin derivative	Similar to amoxicillin/clavulanate
		Tazobactam sodium (used clinically with piperacilllin)	Semi-synthetic penicillin derivative	Tazobactam/piperacillin effective against intra-abdominal infections
	Vancomycin	Vancomycin	*Strep. orientalis*	Introduced in 1956; used against staphylococcal and enterococcal infections
	Teicoplanin	Teicoplanin	*Actinoplanes teichomyceticus*	Experimental in the U.S., available for compassionate use
	Vancomycin derivatives with catalytic activity		Semi-synthetic	Experimental

(continued)

TABLE 1-2: Antibiotics in Use and Under Development (Cont'd.)

Action	Family/Class	Example(s)	Source	Status
Antibiotics that increase membrane permeability	Peptides			
	Bactericidal/Permeability Increasing Protein (BPI)		Mammalian cells	Experimental
	Magainins		African clawed frog	Experimental
	Cecropins		Silk moth, other insects, mammals	Experimental
	Defencins		Mammalian cells	Experimental
	Steroids		Dogfish sharks	Experimental
Metabolic interference	Sulfonamides	Sulfamethoxazole	Azo dyes	In use since 1930s; first antimicrobial agent used in man
	Trimethoprim	Trimethoprim	Synthetic	Synthesized in 1968, commonly used together with sulfanimides
Protein synthesis inhibitors	Aminoglycosides	Streptomycin Kanamycin Tobramycin Gentamicin	*Streptomyces griseus* *Streptomyces kanamyceticus* *Streptomyces tenebrarius* *Micromonspora purpurea* and *echinospora*	In use since 1940s; important class of antibiotics
	Fusidanes	Fucidin	Sodium salt of fusidic acid, derived from the fungus *Fusidium coccineum*	In clinical use since 1962, but not available in US (except through compassionate release); active against some strains of methicillin-resistant *Staph. aureus* (MRSA)
	Tetracyclines	Chlortetracycline Oxytetracycline Minocycline Doxycycline	*Streptomyces aurofaciens* *Streptomyces rimosus* Semi-synthetic derivative Semi-synthetic derivative	First introduced in 1948, found by screening soil samples for antibacterial activity

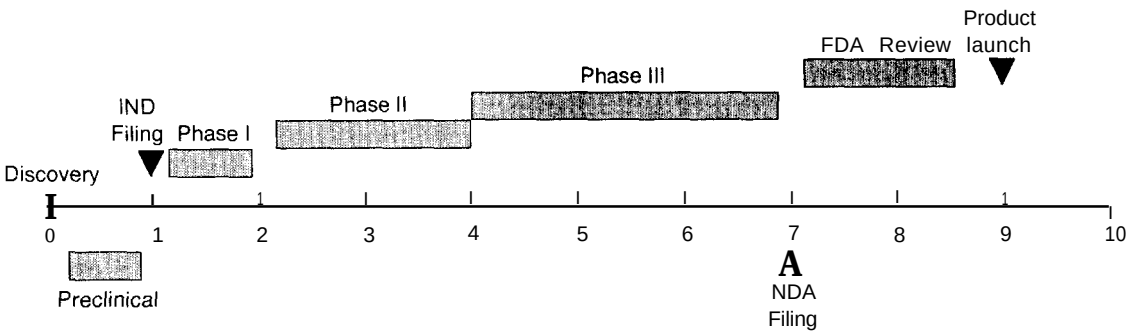
(continued)

TABLE 1-2: Antibiotics in Use and Under Development (Cont'd.)

Action	Family/Class	Example(s)	Source	Status
	Chloramphenicol	Chloramphenicol	*Streptomyces venezuelae*	First introduced in 1949, currently second line antibiotic because of side effect of aplastic anemia
	Macrolides Azalides	Erythromycin Azithromycin	*Streptomyces erythreus* semi-synthetic derivative of erythromycin	Discovered in 1952 Available in 1992
	Lincosamides	Clindamycin	Semi-synthetic derivative of lincomycin derived from *Streptomyces lincolnensis*	Available since the mid 1960s; active against aerobic bacteria
	Mupirocin	Mupirocin	*Pseudomonas fluorescens*	Introduced in the mid 1980s; topical antibiotic
Interference with RNA synthesis	Rifamycins	Rifampin	*Streptomyces mediterranei*	First isolated in 1957, important tuberculosis drug
Toxic effect through DNA binding	Nitroimidazoles	Metronidazole	Synthetic	Introduced in 1959, active against anaerobes such as *B. fragilis*
Block DNA replication or RNA transcription	Antisense nucleotides		Laboratory	Experimental
DNA replication	Quinolones Fluoroquinolones	Nalidixic acid Ciprofloxacin, Ofloxacin	Semi-synthetic	First identified in 1962 Usage began in 1980s; some of the most widely used antibiotics
Anti-tuberculosis drugs		Isoniazid (INH) Pyrazinamide (PZA)	Synthetic Synthetic	Shown to be effective in 1952 Important tuberculosis drug since 1980
		Ethambutanol	Synthetic	Important tuberculosis drug since 1974
Decoy receptors	Carbohydrates		Laboratory	Experimental

SOURCE: Office of Technology Assessment, 1995.

FIGURE 1-3: Approximate Time Line for the Development of a New Antibiotic



KEY: IND = investigational new drug; NDA = new drug application.

SOURCE: Gootz, 1990,

from use opens up markets for new drugs. OTA estimated that a new antibiotic that was limited to the treatment of MRSA has a maximum potential market of about $60 million annua11y,[3] a relatively small market for a pharmaceutical. Ironically, if strains of MRSA became resistant to vancomycin, the potential market would be a lot larger, since the price of the drug to treat otherwise incurable strains could be set much higher. The current market for a drug to treat MRSA, small in comparison with that of many drugs, would discourage marketing of an antibiotic only for MRSA infections. Since the antibiotic would probably be effective against bacteria that cause upper respiratory infections or middle ear infections, it would almost certainly be prescribed for other conditions, increasing the potential markets, and, at the same time, increasing selection pressure for the spread of resistance to the drug.

One issue relevant to antibiotics is the possibility of extending a period of market exclusivity to the manufacturer of an antibiotic in exchange for targeted, restricted marketing of the drug for only particular, specified infections. The restricted marketing would arguably prolong the useful life of the drug by reducing the emergence and spread of bacteria resistant to it (see options).

CONCLUSIONS

The problems caused by antibiotic-resistant bacteria can be ameliorated through two major routes: 1) prolonging the effectiveness of currently available antibiotics through infection control and optimal use of existing antibiotics and 2) developing new antibiotics to treat resistant bacteria.

Similar conclusions have been reached before, and the issues that stem from them have also been discussed (table 1-3). In the following section, OTA discusses 10 issues that arise in efforts to reduce the negative impacts of antibiotic-resistant bacteria. For two issues, OTA has no options for action by Congress or other organizations. While providing additional resources to support ongoing activities in vaccines and diagnostic technologies is a possibility, and careful monitor-

[3] Calculated by multiplying the estimated cases of MRSA times the estimated cost of the new drug assuming that the new drug would be priced similar to vancomycin (which is currently used to treat MRSA). The maximum potential market is the market expected if the new drug was used to treat all cases of MRSA. (Note that it is unlikely that a new drug would capture the market so long as vancomycin is still available for and useful in the treatment of MRSA.)

TABLE 1-3: Publications/Articles on Antibiotic-Resistant Bacteria

The problem of antibiotic-resistant bacteria has existed for years, and many articles and publications have discussed issues surrounding the dilemma. The following is a sample listing of some of them. A full bibliography follows.

Year	Author	Issue
1959	Finland, et al.	Antibiotic use and resistance
1973	Kunin, et al.	Problem and solution of antibiotic usage
1979	Buckwold, et al.	Antimicrobial misuse
1985	Burke and Levy	Worldwide antibiotic resistance
1992	Cohen	Epidemiology of drug resistance
1992	Institute of Medicine	Emerging infections
1992	Levy	The antibiotic paradox
1992	Neu	The crisis in antibiotic resistance
1994	Murray	Can antibiotic resistance be controlled?
1994	Tomasz	Multiple-antibiotic-resistant pathogenic bacteria
1995	CISET	Emerging and re-emerging infectious diseases

SOURCES:

Finland, M., et al., "Occurrence of Serious Bacterial Infections Since Introduction of Antibacterial Agents," *Journal of the American Medical Association, 170*:2188–2197, 1959.

Kunin, C.M., Tupasi, T., and Craig, W.A., "Use of Antibiotics: A Brief Exposition of the Problem and Some Tentative Solutions," *Annals of Internal Medicine 79*:555–560, 1973.

Buckwold, F.J. and Ronald, A.R., "Antimicrobial Misuse—Effects and Suggestions for Control," *Journal of Antimicrobial Chemotherapy 5*:129–135, 1979.

Burke, J.P. and Levy, S.B., "Summary Report on Worldwide Antibiotic Resistance: International Task Forces on Antibiotic Use," *Reviews of Infectious Diseases 7*:560–564, 1985.

Cohen, M.L., "Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era," *Science 257*:1050–1055, 1992.

Institute of Medicine, *Emerging Infections: Microbial Threats to Health in the United States*, J. Lederberg, R.E. Shope, S.C.J. Oaks (Eds.), 1992.

Levy, S.B., "The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle," 1992.

Neu, H.C., "The Crisis in Antibiotic Resistance," *Science 257*:1064–1073, 1992.

Murray, B.E., "Can Antibiotic Resistance Be Controlled?" *New England Journal of Medicine 330*:1229–1230, 1994.

Tomasz, A., "Multiple-Antibiotic-Resistant Pathogenic Bacteria—A Report on the Rockefeller University Workshop," *New England Journal of Medicine 330*:1247–1251, 1994.

Executive Office of the President, National Science and Technology Council, Committee on International Science, Engineering, and Technology Working Group, *Emerging and re-emerging infectious diseases: global microbial threats in the 1990s*. (Washington, DC: 1995).

ing and oversight of federal programs and their progress are important, no options for such incremental changes are presented. For the remaining issues, OTA proposes one or more options. Some of these options would involve greater research support by the federal government, and OTA underlines the reasons for such support and, in some cases, why it is expected to bring savings in costs. Box 1-3 contains an outline of the issues and options. All of these efforts will have to be sustained, as the quote in box 1-4 underlines.

ISSUES AND OPTIONS FOR PROLONGING EFFECTIVENESS OF ANTIBIOTICS

Issue A: Surveillance

If officials decide to design a nationwide surveillance system, they must resolve many issues before its implementation. Often, Congress or an executive branch agency turns to a commission or panel to make recommendations, and any such group could be instructed to consider the following questions in the design of a national surveillance system.

BOX 1-3: Conclusions, Issues and Options

The problems caused by antibiotic-resistant bacteria can be ameliorated through the major routes:

1) prolonging the effectiveness of currently available antibiotics through infection control and optimal use of existing antibiotics, and

2) developing new antibiotics to treat resistant bacteria.

Issues that arise in efforts to prolong the effectiveness of currently available antibiotics:

Issue A: Surveillance

Option 1: Congress could support the establishment of a national surveillance system, including providing funding.

Issue B: Vaccines

Issue C: Infection control

Option 2: Congress could encourage all States to adopt guidelines for the coordination of infection control measures between acute care and long-term care facilities and to include all antibiotic-resistant bacteria.

Option 3: Hospitals should consider instituting antibiotic-use subcommittees in their infection control committees.

Issue D: Research funding

Option 4: Congress can make money available for studies of the development, transfer, and persistence of antibiotic resistance.

Option 5: Congress can make money available for research into the basic biology of bacteria.

Option 6: Congress can make resources available for the study of appropriate use of devices that present infection risks to hospitalized patients.

Issue E: Diagnostic technologies

Issue F: Controlling antibiotic use

Option 7: Review Medicare and Medicaid reimbursement policies for their unanticipated effects on antibiotic prescription patterns.

Issue G: Antibiotics in animal husbandry

Option 8: Collect information about associations between animal husbandry uses of antibiotics and antibiotic-resistant bacteria in humans.

Option 9: Design a study to determine the sources of antibiotic-resistant bacteria in the human diet.

Option 10: Study the benefits of antibiotic use in animal husbandry.

Issues that arise in efforts to develop new antibiotics:

Issue H: Cooperative research among government, industry, and academia

Option 11: NIH could solicit applications for grants to fund cooperative research between universities and pharmaceutical firms to discover new antibiotics.

Issue I: Negotiated marketing agreements for antibiotics

Option 12: Congress can provide FDA with authority to negotiate extended market exclusivity to manufacturers that agree to restrictions on marketing of antibiotics.

Issue J: Development of off-patent compounds as antibiotics

Option 13: Congress could authorize FDA to extend market exclusivity for “off-patent” antibiotics that are shown to be effective against antibiotic-resistant bacteria.

Option 14: Congress could provide research support for a federal program to conduct clinical trials of antibiotics to determine if they have uses against antibiotic-resistant bacteria.

BOX 1-4: The Myth of Sisyphus and Antibiotics

"The search for and development of new drugs by the pharmaceutical industry will go a long way toward conquering the growing microbial resistances to available antibiotics. But there is much more to be done than merely generating new antibiotics—the pace of which cannot keep up with the microbial resistance responses....

"The history of antibiotics reminded our student Raul Borbolla of the Greek myth of Sisyphus, the king of Corinth who, as punishment for his hubris, was condemned by the gods to push a boulder up a mountain, only to have the boulder roll to the bottom, from which Sisyphus had to start pushing again. Again the boulder would roll to the bottom, and the cycle was repeated into perpetuity. The rational and controlled use of antibiotics may prevent medicine from facing Sisyphus's fate."

SOURCE: C.F. Amabile-Cuevas, M. Cardenas-Garcia and M. Ludgar (1995), *American Scientist 83*:320–329.

- *Which antibiotics and organisms will be included in the system?* There are more than 100 different antibiotics and many possible organisms, and it will be impossible to maintain surveillance of all "drug-bug" combinations. Some regional adjustments might be considered because of geographical variations in antibiotic usage.
- *How many hospitals and laboratories will participate in the system?* Will all participate, or will a representative sample of hospitals and laboratories comprise the network?
- *What kinds of laboratory-determined data will be incorporated into the system?* This will be a major issue in any surveillance system for antibiotic-resistant bacteria because of the variety of techniques already available and the major changes in diagnostic technologies that are now underway.
- *How will the system assure the quality of test results?* Would the surveillance system collect raw data as WHONET does? Or insist on use of standard guidelines to interpret the data? Who would develop the guidelines? How would results from genotypic tests, which directly measure the presence of a gene for resistance, be compared to phenotypic tests, which measure the ability of the bacteria to survive in the presence of an antibiotic?
- *Who will have access to the system*? Will access be restricted to the medical community, or would others, such as pharmaceutical companies and private computer owners, be able to gain entry to the system?
- *Would banking of samples be part of the system?* Some small, currently operating systems collect and bank some bacterial samples to allow rechecking of identification. Would pharmaceutical companies be provided access to banked samples to test new antibiotics?
- *Will hospitals link pharmacy records, patient data, and laboratory information?* This linkage would be ideal, because it would allow researchers to correlate data about the effect of antibiotic usage and resistance directly and to correlate clinical outcomes with test data.
- *Should the system be extended internationally?* Antibiotic-resistant bacteria travel from country to country, posing an international problem. Therefore, it may be in the best interest of the U.S. to include other countries in a surveillance system. How would this be done?
- *What role would surveillance system personnel take in training of hospital personnel to use the results of the surveillance system?* The success of the system will depend on the use that is made of its results, and system personnel may have to devote some time to make sure the results are well used.

The cost of the system will have to be considered. The more complex the system, the more it will cost. However, some successful surveillance systems, such as WHONET and the New Jersey State System, have been built on very small bud-

gets. The CDC estimates that bringing their DRSP system to each state would require start-up costs of about $200,000 for each state, for a total of $10 million and annual operating costs between $2.5 and $5 million. If a surveillance system prevents even 1 percent of infections caused by antibiotic-resistant bacteria (which OTA estimates cost a minimum of $1.3 billion per year in 1992 dollars), the system would pay for itself.

An alternative to surveillance systems is a program to investigate outbreaks of infectious diseases as they are reported. A difficulty with the alternative is that in the absence of a surveillance system, not all cases will be reported to health officials. According to CDC, 27 illnesses caused by *E. coli* O157:H7 were confirmed in New Jersey in June 1994, compared to five cases in the same period in 1993. This "pseudo-outbreak," as CDC called it, resulted from better reporting as a result of institution of a surveillance system that required laboratory testing of some clinical laboratory samples for the *E. coli*. It illustrates that many opportunities to intervene and disrupt transmission of infectious diseases can be missed without a surveillance system.

OPTION *Congress could support the establishment of a national surveillance system, including providing funding.*

A surveillance system is essential for understanding the spread of antibiotic-resistant bacteria and planning interventions so as to preserve the efficacy of currently available antibiotics. Because of these public health considerations, and the likelihood that a surveillance system would decrease medical costs, including costs to Medicare, Congress could consider funding a nationwide surveillance system.

The features of current, limited systems can be incorporated and combined to produce a system of desired size, complexity, and cost. It may be advantageous to begin with a less complex system (such as some of the operating systems described in this report), and then add more features. Any system must have a strong advisory group that includes diagnostic laboratory and computer experts, clinicians, hospital administrators, pharmaceutical company researchers, academic scientists, and federal and state regulatory and health officials. The advisors could work to assure that the surveillance system collects and disseminates the information in the forms for its best use.

Issue B: Vaccines

The biotechnology revolution is expected to produce many new potential vaccines. This would be a welcome change from the slow rates of discovery and development of recent years, and it will benefit from and may, indeed, require new mechanisms for vaccine testing, development, and approval. If this effort is successful, effective vaccines would reduce the need for some antibiotics and would, therefore, help control antibiotic resistance.

The private sector conducts much of the current vaccine research, but current federal policies restrict the income from vaccines sales, and that may inhibit research activities. To provide low-income Americans with vaccines, the federal government now purchases up to 80 percent of all vaccines at a fixed, low price. GAO, however, reports that the price of vaccines for children has little effect on vaccination rates, largely because poor children are entitled to free vaccine. As Congress considers the Vaccines for Children program, it can be expected that vaccine manufacturers will argue that the price cap and reduced profits have created an adverse effect on new vaccine development. Determining the impact of the price cap on research could be an objective of the congressional inquiries.

GAO describes efforts that have fallen short in reaching various federal goals for immunization rates. Although Medicare pays for the administration of pneumococcal vaccine to the elderly, 73 percent of them have never received it. That and other observations made by GAO indicate that there is much to be done to increase vaccination rates, and the reports make some suggestions.

Encouragement of adult vaccination deserves special consideration in light of changes around the world. Currently, diphtheria is epidemic in Eastern Europe, and as many as 50 percent of United States adults over 30 are susceptible to that disease because they have not had immunization booster shots. Since 1988, the few confirmed cases of diphtheria in the United States have been related to importation of disease from other countries, illuminating the international nature of the spread of infectious diseases, which can include those caused by antibiotic-resistant bacteria.

Issue C: Infection Control

Several new medical techniques and devices are designed to reduce infections, and private organizations, such as insurance companies and hospitals, have a financial incentive to institute effective infection control procedures that can save money, reduce hospitalization rates, and help control antibiotic-resistant bacteria. The government, acting as an insurer through Medicare and Medicaid, may also have an interest in funding research to develop new techniques and methods and to apply them.

Some devices and techniques that reduce infection rates are available, and their adoption has been demonstrated to reduce in-hospital time and costs. Most importantly, the patients benefited from fewer hospitalizations. Nevertheless, adoption of such improvements may hinge on events as distant as Medicare reimbursement procedures. Medicare reimburses dialysis centers and hospitals separately, and there is no financial incentive for dialysis centers to invest in these new technologies.

The Joint Commission for the Accreditation of Health Care Organizations (JCAHO) is beginning to collect data on infection control from hospitals on a voluntary basis, with about 400 hospitals now participating. Analysis of these data may be a very useful tool in understanding the differences between successful and not-so-successful infection control in hospitals. This program provides limited information; it is not mandatory and it collects no data on antibiotic resistance. Nevertheless, it provides information for research efforts, and it can be expanded.

With recent changes in the health care system, hospitals discharge many patients more quickly than in the past, and many patients are moved to long-term care facilities. Some of these patients, when discharged to the long-term facilities, have active infections or are at high risk for infection because of indwelling invasive devices such as catheters or intravenous lines or because they are on dialysis. Further, the large concentrations of antibiotics used in these facilities (like the large concentrations used in hospitals) selects for the emergence and spread of antibiotic-resistant bacteria, as is demonstrated by the high prevalence of MRSA in nursing homes. Patients infected with antibiotic-resistant bacteria in nursing homes frequently return to the hospital, where the antibiotic-resistant bacteria can spread further.

OPTION *Congress could encourage all states to adopt guidelines for the coordination of infection control measures between acute care and long-term care facilities and to extend guidelines to include all antibiotic-resistant bacteria.*

Many state health departments have recognized the problems of transfer of MRSA between hospitals and long-term care facilities and have published extensive guidelines for coordination of the admission, discharge and transfer of MRSA-colonized patients between two facilities. Wider adoption of these procedures should reduce the transmission of infections caused by antibiotic-resistant bacteria (and other bacteria) while simultaneously lowering costs and optimizing patient care.

OPTION *Hospitals should consider instituting antibiotic-use subcommittees in the infection control committees.*

Every hospital has an infection control committee. Assigning a subcommittee responsibility for monitoring antibiotic use and relating that use to the spread of antibiotic-resistant bacteria

would focus attention on these problems and bring them to the attention of hospital staff.

Issue D: Research Funding

The current federal belt-tightening era has produced a reluctance to commit new sums of money to research, which may make it necessary to transfer money from other research areas to support research related to antibiotic-resistant bacteria. Such decisions are difficult, but without additional research support, the country may fall further behind in trying to counter antibiotic-resistant bacteria. One consequence of increased support of such research will be the training of scientists and physicians in skills necessary to teach others the newest methods in research and in the application of research findings.

OPTION *Congress can make money available for studies of the development, transfer, and persistence of antibiotic resistance.*

Scientists understand the basic principles of the emergence and spread of antibiotic resistance and of the genetic transfer of resistance between bacteria, but they do not have enough details to predict how the patterns of use of antibiotics will affect the prevalence of resistance genes. For example, restricting the use of an antibiotic often leads to a decrease in the prevalence of antibiotic resistance. That would appear to pave the way for reintroducing the antibiotic, but it is uncertain what will happen when the antibiotic is reintroduced because the time course for the reappearance of resistance is unknown.

OPTION *Congress can make money available for research into the basic biology of bacteria.*

The molecular organization and function and the biochemistry of bacteria differ from those of animal and human cells, and pharmaceutical companies have exploited those differences in developing antibiotics. Basic research directed at better understanding of bacterial biochemistry may reveal new targets for antibiotics; in any case, it will produce information that will be useful in understanding bacterial growth and pathogenesis.

The amounts of federal money spent on non-AIDS research have not increased in parallel with the increasing inroads being made by antibiotic-resistant bacteria. For instance, the federal government gave CDC a $6.7 million increase in its non-AIDS budget specifically to combat emerging infectious diseases. However, only about 10 to 15 percent of that money will be used for antibiotic resistance, and it is unclear how much of that amount will be used for research. Relatively small increases, a few million dollars in the total federal budget directed at antibiotic-resistant bacteria, could produce a marked increase in the amount of research being done.

OPTION *Congress can make resources available for the study of appropriate use of devices that present infection risks to hospitalized patients.*

Many nosocomial infections result from the use of invasive devices such as catheters and mechanical ventilators, often routinely used in intensive care units. There is little research about when such devices improve outcomes. Such research will probably not be funded by manufacturers that benefit from the sales of equipment. Learning about the risks and benefits of these devices may depend on government funding. This information would guide decisions about when to use these devices, probably reducing their use (and associated costs) and reducing infection rates.

Issue E: Diagnostic Technologies

The most powerful weapon in the arsenal directed at antibiotic-resistant bacteria are techniques for the rapid and accurate identification of bacteria and determination of their susceptibility to antibiotics. New techniques are necessary. When available, they will provide the most certain information for appropriate antibiotic use.

The lack of rapid in-office methods to screen for and to identify bacteria and to characterize their antibiotic-resistance patterns probably reinforces physicians' tendency to prescribe broad-

spectrum antibiotics for presumed bacterial infections. As quicker tests become available, some of which are likely to be quite simple to perform and present few problems in interpretation, more conflicts are expected between the provisions of the Clinical Laboratory Improvement Act (CLIA) and physicians' desires to use the new tests. CLIA requires that physicians register their offices and fulfill (largely record-keeping) requirements in order to carry out laboratory tests. One solution to the conflict is to excuse physicians' offices from CLIA, and legislation has been introduced to exempt clinical laboratories in physicians' offices from having to comply with CLIA regulations.

Another way to improve the use of diagnostic tests in physician offices would be encouragement of manufacturers to develop test kits to meet the performance specifications for products in the "waived" category of tests under CLIA. This would preserve the positive effects of CLIA. For example, CLIA has had a positive effect on the way tests are manufactured: many currently waived tests contain built-in controls to comply with CLIA. These controls make it easier for the person performing the test to determine whether it has been performed correctly. CDC, which determines the categorization of tests under CLIA, has already taken steps in this direction by sending a letter to manufacturers to inform them of the possibility of including their tests in the waived category and outlining the requirements for tests in this category. Groups such as the American Medical Association could determine which tests are most useful for physician offices and work together with the manufacturers and CLIA administrators to provide tests suitable for the waived category.

With no action taken at all, potential conflicts between physicians' desires to carry out in-office tests and CLIA will diminish. Over the next few years, group practices that develop sufficient test volumes to require comprehensive laboratories will seek CLIA approval as a matter of course. Smaller offices, however, will persist in rural areas, and CLIA may be more of an issue in those locations.

The term "service labs" is generally used to refer to laboratories in hospitals or to commercial laboratories that identify and characterize bacteria and other infectious organisms. In a draft report about a new surveillance system for antibiotic-resistant *S. pneumoniae* (see option 1), CDC states that laboratories may not be using the most up-to-date standards. CDC suggests that the National Committee for Clinical Laboratory Standards (NCCLS) guidelines could be published in the *Morbidity and Mortality Weekly Report (MMWR)* and as letters to clinical laboratory journals to inform both physicians and laboratories about appropriate standards. This seems a reasonable step. Since CDC publishes *MMWR*, it should be able to disseminate the guidelines through that publication.

New diagnostic technologies, such as those based on DNA identification, have advanced rapidly, but regulatory procedures have not kept abreast of the new technologies. This slow pace has resulted in conflicting signals about the use of the tests, which can be illustrated by the case of tuberculosis diagnostic tests. The public health benefits of rapid and specific diagnostic tests include reducing the transmission of tuberculosis through optimal use of the few beds reserved for tuberculosis patients and the better treatment of infected individuals, reducing unnecessary use of antibiotics and the resulting selection for resistant bacteria. Many hospitals in areas with high tuberculosis rates currently rely on DNA diagnostic tests for these applications.

Despite the great advantage in speed and the current use of such tests, CDC and the FDA have advised that physicians should use conventional methods until DNA techniques are better defined. Even so, conventional tests are not without problems. Culture tests for tuberculosis are difficult to perform accurately and obtaining reproducible results is difficult. Also, different testing laboratories have produced conflicting results in measuring susceptibility to the tuberculosis drug pyrazinamide, demonstrating that conventional tests are not without problems.

Even in the absence of a CDC approval of the new DNA-based tests, some private insurers will

pay for them. However, tuberculosis is a disease that disproportionately affects poor people, and Medicare and Medicaid coverage of these procedures would improve those people's access to these methods. Such coverage would result in health benefits of prompt treatment and reduced transmission of tuberculosis to health care workers and the community.

To date, the FDA has not approved a kit for tuberculosis testing. However, some service laboratories perform tests using devices of their own making or devices that are licensed for research but not clinical applications. There are, however, no guidelines for proficiency testing of laboratories. The adoption of guidelines for ensuring proficiency testing of laboratories performing new tests should be a priority of government organizations such as CDC. In this way, access to and quality of new diagnostic technologies can be maximized.

Service labs are likely to face these difficulties for many tests. Some bacteria are so rare that no test kits will ever be made to identify them; the market is too small. But microbiology service labs will devise their own tests, and those tests will raise many of the same issues as the issues raised by new tuberculosis tests.

Issue F: Controlling Antibiotic Use

Numerous organizations, including state and federal agencies, insurance companies, and health professional associations, have developed practice guidelines that address a range of clinical conditions. Practice guidelines might influence the use of antibiotics.

For example, a physician considering whether or not to prescribe an antibiotic may decide to do so because of a possible malpractice action if he or she does not and the patient fails to improve. The physician might want to rely on a practice guideline as an authority for the decision he or she made, but it might not be sufficient defense in a malpractice suit. Currently, the use of practice guidelines in medical malpractice litigation is a complicated and controversial issue. Moreover, guidelines may actually have the effect of encouraging the use of antibiotics because a guideline which admits any benefit of the use of antibiotics for a specific illness may be used as evidence against a physician who chose not to prescribe antibiotics.

Hospitals use formularies to restrict the number of antibiotics available and that can require approval by an infectious disease specialist for use of some antibiotics. A 1994 review of these restrictive measures documented reduced expenses for antimicrobial acquisition and administration, reduced adverse drug reactions in a limited number of cases, and improved appropriateness of drug choice. It also found disadvantages, including difficulties of implementation in the community hospital setting, inconvenience for the prescribing physician, and increased administrative costs. Antibiotic control programs were associated with a decrease in antibiotic resistance in a few hospitals, but disappointingly, the resistance increased "abruptly when control or monitoring was relaxed or removed." This phenomenon suggests that permanent control or monitoring is necessary for prolonged decreases in antibiotic resistance.

Change of at least one federal policy might reduce the use of vancomycin, the antibiotic of last resort in some infections.

OPTION *Review Medicare and Medicaid reimbursement policies for their unanticipated effects on antibiotic prescription patterns.*

Medicare generally does not pay for intravenous medications in the home but does pay for medications that require the use of an infusion pump. This policy has caused some physicians to prescribe vancomycin, which requires the use of an infusion pump and therefore is covered under this policy, rather than other antibiotics that are not covered. This policy runs counter to CDC's recommended judicious use of vancomycin. Should Medicare change this policy, it may also influence private insurers to consider unanticipated effects on antibiotic prescription patterns, and there may be other examples of policies having such undesirable effects on antibiotic use.

Issue G: Antibiotics in Animal Husbandry

The overriding uncertainty about agricultural uses of antibiotics is their contribution to antibiotic-resistant bacteria and to complications in the treatment of human diseases. **Years of expert review testify to the difficulty of coming to any generally accepted conclusions about the effects of long-term, low-level feeding of antibiotics to food animals and the appearance of antibiotic-resistant bacteria in humans (see chapter 7), and it is unreasonable to expect that another review of existing data would provide resolution.** The following three options, if adopted, would provide for the collection of new information. Importantly, however, careful analysis needs to precede any study because it is quite possible that no study can produce information sufficiently definitive to justify the expense of the study, and that analysis would have to involve agricultural interests, pharmaceutical companies, farmers, farmers organizations, public health officials, environmental organizations, organic food processors, and scientists from all those organizations as well as universities and the government. All have a stake in any study about antibiotic use in animal husbandry.

OPTION *Collect information about associations between animal husbandry uses of antibiotics and antibiotic-resistant bacteria in humans.*

Any serious study of the risks from animal husbandry uses of antibiotics will require the expertise of epidemiologists, and many of those scientists are at the CDC. Congress could provide money to CDC to convene a group of scientists to examine the prospects of designing a study about the transfer of antibiotic-resistant bacteria from animals to humans. The scientists, representing all the interests involved in this issue, would be required to estimate the cost and time necessary for the study and the size of the impact that they can detect. For instance, would it be possible to design a study to answer the question: "Does agricultural use of antibiotics contribute 2 (or 5, or 10) percent of the antibiotic-resistant bacteria in humans?"

One possible outcome of the scientists' deliberations would be the conclusion that the study could not provide any certain information. FDA, in making comments on an earlier draft of this report, said it is convinced that such a study cannot be done, and OTA's 1993 assessment *Researching Health Risks* discusses the difficulties of investigations of environmental health risks; some of those are applicable here. A decision that the study would not answer the questions could be accompanied with advice about what new techniques might alter the decision in the future.

If this study were undertaken, a study of gene transfer from bacteria from food animals to bacteria important to human health could be built into it.

OPTION *Design a study to determine the sources of antibiotic-resistant bacteria in the human diet.*

A study to investigate the sources of antibiotic-resistant bacteria need not be so demanding. It could be designed to collect a sample of marketed foods, isolate bacteria from the foods, and characterize their antibiotic resistance. The characterization could be done at the molecular level to determine the source of the bacteria.

The successful completion of this study would be informative about the levels and perhaps sources of antibiotic-resistant bacteria in common foods. That information might lead to interventions in some food handling processes to reduce bacterial contamination, and it might lead to consumers' being more careful in food preparation. On the other hand, since it is well-known that food poisoning is a risk and people take precautions against it, the information about transfer of antibiotic-resistant bacteria might have no or few effects on behavior.

OPTION *Study the benefits of antibiotic use in animal husbandry.*

Reviews of the information about health impacts of antibiotic use in animal husbandry often point to possible risks. Statements about risk are often countered by claims that the benefits of continued use of antibiotics for growth promotion outweigh the risk, and farmers' continued use of subtherapeutic doses is offered as evidence for those benefits.

An analysis of written information could probably determine the costs of the antibiotics in feeds. It might also be possible to determine the benefits of their use from the literature. More likely, however, some feeding experiments would be necessary to make quantitative determination of the benefits as measured by increased yields. This information about benefits could be considered in efforts to sort out the costs and benefits of subtherapeutic doses of antibiotics.

ISSUES AND OPTIONS FOR ENCOURAGING DEVELOPMENT OF NEW ANTIBIOTICS

Until recently, new antibiotics had been developed at such a rate that no bacteria were resistant to all of them. Today, this is no longer true.

Manufacturers develop antibiotics in anticipation of markets and profits. In the 1980s, the market was saturated with more than 100 antibiotics, which reduced the profit to be expected from yet another entry in a crowded field. Although research and development expenditures in pharmaceutical companies greatly increased in the 1980s, the percentage of research and development devoted to anti-infectives decreased. Because of the long times necessary for discovery, testing, and development of new drugs, the decisions in the 1980s account in part for the shortage of new antibiotics in the 1990s. Reports of pharmaceutical companies hiring new senior-level scientists for antibiotic research and the interest of many biotechnology companies in antibiotics indicate that they now see opportunities in antibiotic development (see box 1-5), but consolidations and purchases of pharmaceutical firms have also reduced the number and size of research departments and the number of industry-employed scientists devoted to antibiotics.

Because of the importance of drugs to public health, Congress has provided assistance and incentives to pharmaceutical companies, including tax credits for research, increased patent life to compensate for the years of patent protection lost to regulatory delays, a commitment to more rapid review of new drug applications at the FDA, and active technology transfer of drugs developed in whole or in part by government scientists. These tax, patent and research and development policies are discussed in chapter 5 of this report, and in detail in the 1993 OTA report *Pharmaceutical R&D: Costs, Risks and Rewards.* Here OTA considers four options directed specially at antibiotics.

Issue H: Cooperative Research Among Government, Industry, and Academia

The National Cancer Institute (NCI) has funded the National Cooperative Drug Discovery Program since 1983. The program solicits applications from consortia of university researchers and pharmaceutical companies to search for new anti-cancer drugs. The awards are limited to the support of pre-clinical research. Generally, the principal investigator is from a university with co-principal investigators from industry. While the research can take different directions, it generally involves university researchers doing basic research, and industry scientists developing methods for widespread application of the research methods. Through the end of 1994, NCI had invested about $100 million in this program, and several compounds discovered in the program-sponsored research have entered clinical trials.

BOX 1-5: Industry-Funded Cooperative Research

"The Action TB Initiative is an international 5-year programme of collaborative research sponsored by Glaxo. The ultimate objective from Glaxo's point of view is to discover ways to produce new anti-tuberculosis medicines and vaccines....

"In the UK, an ambitious research programme is being pursued under the initiative at centers in London and Birmingham, and scientists at Glaxo are conducting their own research in collaboration. In South Africa, the Medical Research Council is coordinating research programmes at various institutes throughout the country. At the London School of Hygiene and Tropical Medicine, a wide-ranging programme was initiated in July, 1993....

"Apart from the scientific progress achieved already, tangible benefits for the London School have included laboratory renovations and the appointment of new staff. The three project supervisors in London each have their counterpart at Glaxo, and the scientist-to-scientist collaborations are deemed valuable. At this juncture skeptics might reasonably ask 'what's in this for the company?'. Clearly short-term goals have been eschewed, but as a public relations exercise the initiative is unquestionably a success. Moreover, Glaxo has by this means secured an impressive array of medical research expertise to sharpen its competitive edge. Although not all academic researchers would feel comfortable with such an arrangement, as an example of an effective partnership between the pharmaceutical industry and academic health sciences it has much to offer."

SOURCE: *Lancet* (May 13, 1995)

OPTION *NIH could solicit applications for grants to fund cooperative research between universities and pharmaceutical firms to discover new antibiotics.*

The National Institute of Allergy and Infectious Diseases (NIAID) could develop a similar program for antibiotics. Such an effort would have the advantages of forging relationships between university and industry researchers, increasing the speed of dispersion of "academic" ideas to industry, and producing a community of university-industry research groups that could speed up drug discovery. Moreover, such joint research activities would quickly deliver promising substances to pharmaceutical company scientists who could evaluate them against criteria for pharmaceuticals: penetrability, toxicity, specificity, and bioavailability.

There are disadvantages as well. It is unlikely that additional money will be provided to NIAID in the near future, and in FY 93, NIAID spent about $10 million on research directed at antibiotic resistance, which is about the average annual amount spent by NCI on its Cooperative Drug Discovery Program. To set up an expensive antibiotic discovery program would require diverting funds from other research programs. This may not be the optimal use of limited government funding for research, especially in light of basic research needs for which industry support is unlikely (see Issue D).

Issue I: Negotiated Marketing Agreements for Antibiotics

A pharmaceutical company that discovers and develops an antibiotic that is effective against particularly troublesome antibiotic-resistant bacteria as well as against many other bacteria might be willing to restrict its marketing to use against the antibiotic-resistant bacteria in exchange for longer market exclusivity. The trade-off, simply put, is that 10 years of a protected market might generate as much profit as five years of higher, less-restricted sales that resulted in faster development of antibiotic resistance.

OPTION *Congress can provide FDA with authority to negotiate extended market exclusivity to manufacturers that agree to restrictions on marketing of antibiotics.*

Usually, a drug enjoys an exclusive market until its patent protection expires. The exclusivity means that generic compounds that are identical to it cannot be marketed. Congress has granted FDA the authority to extend the length of exclusivity under certain conditions when a manufacturer shows that its product is safe and effective against a new indication. Congress could extend the same authority to FDA to negotiate agreements for extended exclusivity in exchange for restricting marketing to uses against particular antibiotic-resistant bacteria or against diseases likely to be complicated by antibiotic-resistant bacteria.

The advantage of such an action could be longer effective usefulness of the antibiotics. Moreover, FDA authority to negotiate such arrangements would leave pharmaceutical companies free to consider different marketing strategies and to choose the most beneficial one in terms of profits, public relations, or other factors.

Extended exclusivity would not preclude another company's efforts to develop antibiotics for similar conditions. If the other company produced a comparable or better drug, the company with the extended exclusivity might see its potential profits disappear.

Physicians commonly prescribe drugs "off-label" for indications other than those approved by the FDA and that could weaken the restricted marketing program. On the other hand, exclusivity extensions could include provisions to allow FDA to be certain that companies with such agreements not sponsor research or research dissemination activities that would promote such off-label uses.

An examination of how such a system might have affected the sales of, and the development of resistance to, antibiotics that are no longer of clinical use because of resistance would inform any congressional decision about this option. While pharmaceutical companies might be willing to fund the analysis, public funding might be necessary for a credible study and results.

Issue J: Development of Off-Patent Compounds as Antibiotics

Many chemical compounds were discovered and patented but never developed as pharmaceuticals for various reasons. For instance, a substance with antibiotic activity might not have been brought to market because it was no better than marketed antibiotics against susceptible bacteria or because it was somewhat more toxic than marketed antibiotics. In screening materials for antibiotic activity against antibiotic-resistant bacteria, companies often re-discover such old compounds. Although they might appear promising because of activity against antibiotic-resistant bacteria, no company will do the research and development necessary to bring them to market because patent protection is or soon will be gone.

As an example, fusidic acid is an antibiotic that was never brought to market in the United States but that has been used in other countries, including Canada, for years. It is used in the treatment of MRSA in other countries, but its manufacturer perceives that the return on investment would be too low to warrant pursuing clinical trials for use against MRSA in this country. A licensing agreement with a United States firm faces a similar obstacle; if the trials were successful, any other company could manufacture and sell the off-patent substance, greatly reducing the opportunities for the foreign-United States company venture to recoup its losses and make a profit.

OPTION *Congress could authorize FDA to extend market exclusivity for "off-patent" antibiotics that are shown to be effective against antibiotic-resistant bacteria.*

Such legislation might result in pharmaceutical companies' ferreting out effective antibiotics from the thousands that have been patented, but it would leave FDA with the difficult problem of deciding when the advantages of an antibiotic justified the granting of exclusivity. Market exclusivity is one privilege granted under the orphan drug law, and it is possible that antibiot-

ics that are effective against antibiotic-resistant bacteria would meet the requirements of an orphan drug.

OPTION *Congress could establish a federal program to conduct clinical trials of antibiotics to determine if they have uses against antibiotic-resistant bacteria.*

An antibiotic that is off-patent and manufactured generically could be reported to be active against infections caused by antibiotic-resistant bacteria. No company, however, would be interested in paying for the clinical trials necessary to demonstrate that the drug is useful because it could not expect to reap sufficient profit from sales of a generic drug.

A federal program could be established to conduct such trials. The advantage would be the identification of useful antibiotics. The disadvantage would be the shouldering of clinical trial costs, traditionally the responsibility of pharmaceutical companies, by the government. Moreover, it is possible that such a program, as any research program, might have no successes.

Introduction 2

Many of the organisms living around, on, and in human beings are too small to be seen without a microscope. They include viruses, bacteria, fungi, and protozoa (figure 2-1).

Viruses are short lengths of genetic material—deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)—enclosed in a protein coat. So small that they have no room for the structures and processes for the biochemistry of their replication, viruses are obligate internal parasites. They must invade cells—human, animal, plant, or bacterial, depending on the virus—take over the cells' genetic apparatus, and direct the biochemistry of the cell to produce viral nucleic acid and protein and package them into new viruses.

Bacteria, the single-celled organisms that are the subject of this report, carry the structures and functions necessary for their replication in their cytoplasm. They generally are about one thousandth of a millimeter wide and nearly 500 times smaller than the average animal cell (Watson et al., 1986.). Bacteria are classified as **prokaryotes** because, unlike **eukaryotes,** such as fungi, protozoa, plants and animals, they have no internal membrane (the nuclear envelope) separating their genetic material from other components of the cell (figure 2-2). Bacteria differ from eukaryotes in having some molecular structures and biochemical processes that are absent from eukaryotes or that differ in significant ways from those of eukaryotes. Most antibiotics[1] work by interfering with a structure or process that is present in bacterial and not in other cells. This selectivity accounts for the rarity of serious side-effects associated with most antibiotics; the drugs find no good targets in human (or other eukaryotic cells) and cause few effects there. Figure 2-3 illustrates the differential effects of penicillin on animal cells, which do not have cell walls, and bacteria, which do, and a photo shows the destruction of a bacterial cell by penicillin. **Antibiotics have no effect on viral infections**; viruses use the molecular structures and functions of the infected cells and viral-infected cells offer no targets for antibiotics.

Fungi and **protozoa** are eukaryotes. Antibiotics have no effect on most of these microorgan-

[1] OTA uses the term "antibiotics" to refer to substances that kill or inhibit the growth of bacteria. It is sometimes used to refer to substances that kill or inhibit organisms other than bacteria, but it is used here only to refer to substances with antibacterial activity.

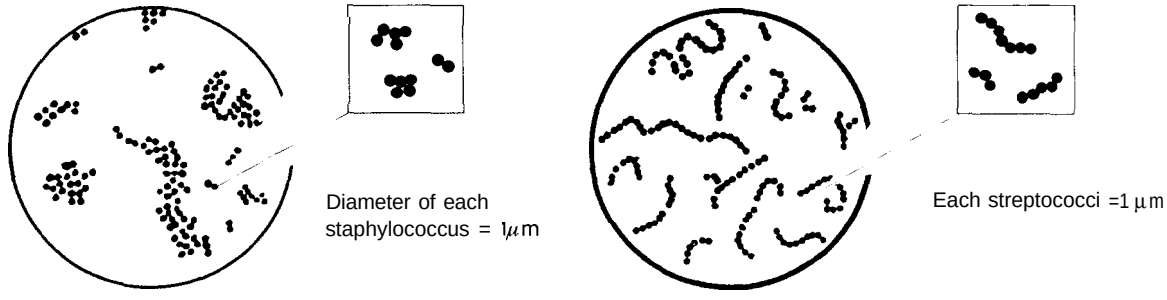
FIGURE 2-1: Infectious Microbial Agents

VIRUSES



Adenovirus (colds) Retrovirus (AIDS) Herpes (fever blisters)

BACTERIA

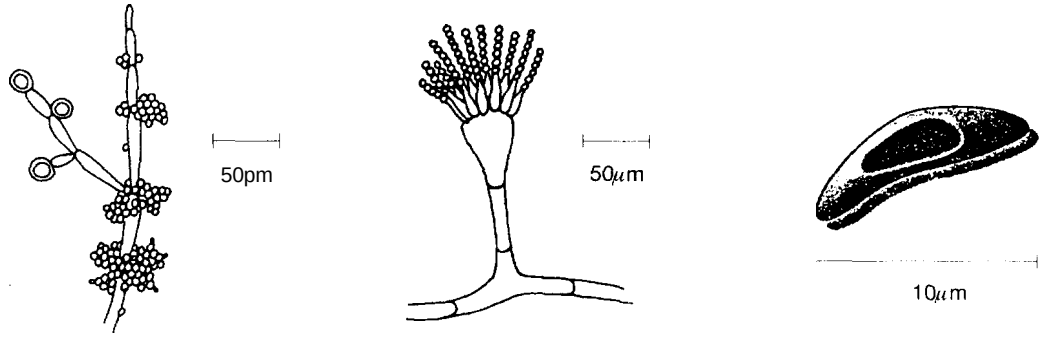


Staphylococci (food poisoning, toxic shock syndrome) Streptococci (pheumonia, rheumatic fever)



Mycobacterium tuberculosis (tuberculosis) Treponema pallidum (syphilis)

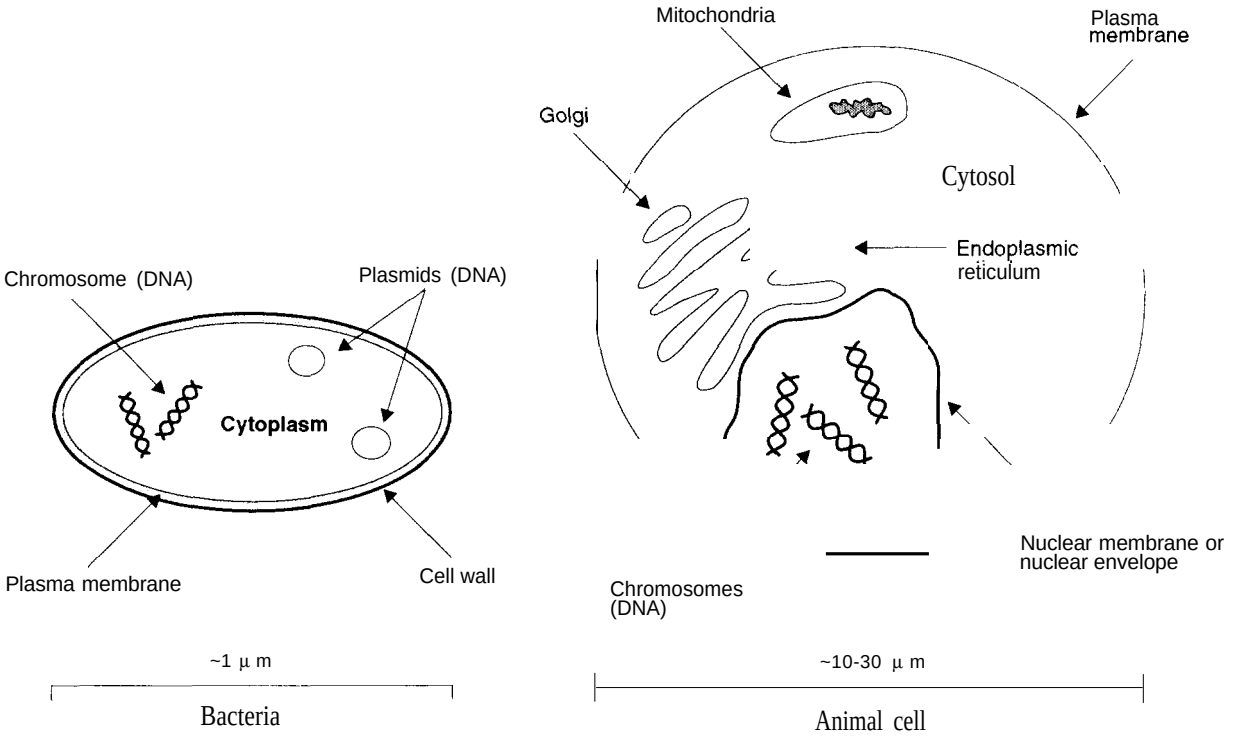
FUNGI PROTOZOA



Candida albicans (yeast infections, thrush) Aspergillus (aspergillosis) Plasmodium (malaria)

SOURCE: Office of Technology Assessment, 1995.

FIGURE 2-2: Simplified Comparison of a Bacterial (Prokaryotic) Cell and an Animal (Eukaryotic) Cell



SOURCE: Office of Technology Assessment, 1995.

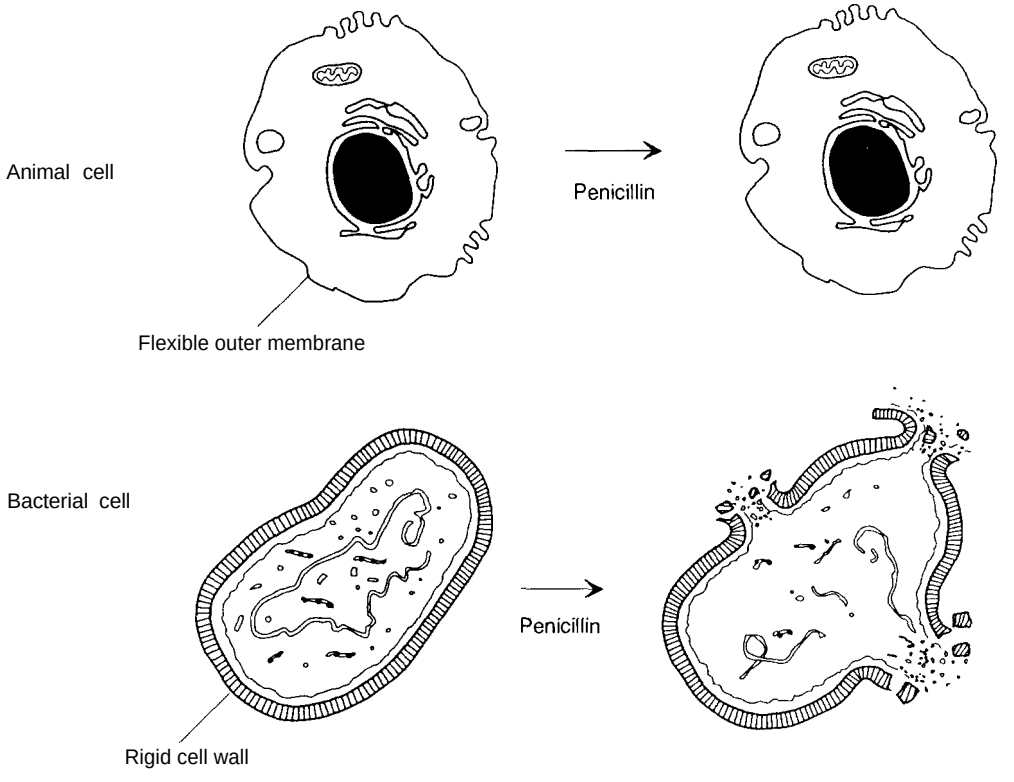
isms. Other chemical agents have been isolated and developed to treat fungal and protozoan infections. Just as with bacteria, which are developing resistance to antibiotics, fungi and protozoae are developing resistance to the drugs used to treat them.

Some bacteria play a role in keeping people healthy. More than 1,000 different species of bacteria normally live benignly in and on the human body. These bacteria, such as *Escherichia coli (see* box 2-1 for a note on bacterial nomenclature) living in the intestine or *Staphylococcus aureus* living on the skin, are called **commensal** organisms. Intestinal bacteria, which are found in concentrations of about 10^{11} (100 billion) bacteria per. gram and account for about 30 percent of the bulk of human feces, produce essential vitamins that are absorbed by the body and provide a barrier against other bacteria becoming established in the intestine. For example, a person may ingest small numbers of a pathogenic Salmonella bacteria but not get sick because the Salmonella is prevented from growing to large numbers by the presence of commensal bacteria in the intestine.

Despite the human body's reliance on bacteria for health, bacteria are far better known as causes of disease. In 1830, infectious diseases caused by bacteria and other microorganisms were a major cause of death, and only 50 percent of the population lived past the age of 25. In the next century, improved sanitation (water purification, sewage systems, pasteurization of milk), general increases in living standards, and the introduction of vaccines reduced the incidence of infectious disease and profoundly changed longevity. By 1935, 50 percent of the population lived past 62 (Schlesinger, 1993).

The capacity of bacteria to cause disease is called **pathogenicity. Virulence** is used as a

FIGURE 2-3: Response of an Animal Cell and a Bacterial Cell to Penicillin



SOURCE: National Institute of General Medical Sciences, Sept. 1993, *Medicines by Design: The Biological Revolution in Pharmacology, NIH* Pub. No, 93-474. Bethesda, MD: National Institutes of Health,

measure of the speed and severity of the resulting disease; more virulent bacteria cause more serious, more rapidly progressing disease, Even commensal bacteria may be harmful under certain conditions. While the skin and mucous membranes normally protect the body from infections, an **opportunistic infection** may result from a bacteria such as S. *aureus* being introduced into the tissues and organs of the body via an open wound, invasive surgery, or use of an invasive device (e.g., a urinary catheter).

Antibiotics often destroy some of the body's commensal bacteria, making way for other infections. For example, the use of some types of antibiotics can allow the organism *Clostridium difficile,* normally present in small numbers in healthy humans, to proliferate and cause the disease pseudomembranous colitis. Yeast infections are common in women treated with antibiotics when antibiotics kill or inhibit commensal bacteria in the vagina. Antibiotics may destroy commensal bacteria in the gut, allowing ingested bacteria, typically resistant to antibiotics, to pervade and cause disease. In two antibiotic-resistant Salmonella outbreaks, it was found that many of the infected people had recently taken antibiotics which may have given the antibiotic-resistant Salmonella an opportunity to become established and cause illness (Holmberg et al., 1984; Spika et al., 1987).

THE DISCOVERY OF ANTIBIOTICS

Before the 1940s, there was little that medicine could do against bacterial infections. Superficial or localized infections could be lanced or surgically opened and cleaned, and locally acting antiseptics could be used to sterilize the area. But once an infection had become "systemic" and



Penicillin-treated bacteria cell bursting at three different places. Photo courtesy of National Institute of General Medical Sciences, National Institutes of Health, Bethesda, MD.

was in the blood stream, little could be done. In World War I, once an infection from even a minor wound developed into dreaded "gas gangrene" (an infection caused by Clostridium bacteria related to the bacteria that cause botulism), there was no treatment except amputation of the wounded limb and prayer that the infection had not reached the soldier's vital organs. People lived in dread that they or their relatives would develop a bacterial pneumonia and die or that a bacterial endocarditis (infection of the heart valves) would doom a child.

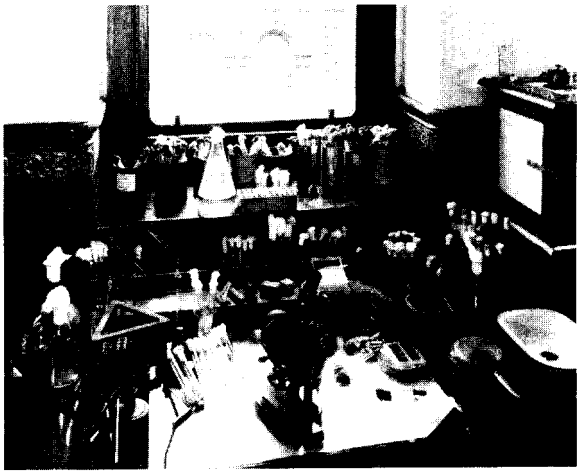
In 1906, chemist Paul Ehrlich provided the first weapon for combating bacterial infection when he discovered that the chemical compound salvarsan was effective against syphilis. In 1936, Gerhard Dogmagk discovered that Prontosil, a synthetic dye, had antibacterial activity. The active chemical component of Prontosil, sulfanilamide, was the first of the sulfonamide (or "sulfa") drugs, and sulfa drugs are still used widely today.

In 1928, Alexander Fleming, an English microbiologist, discovered that a common mold (Penicillium) produced a substance that killed bacteria. Dr. Fleming returned from a weekend

BOX 2-1: Nomenclature

Bacteria and bacterial diseases are our daily companions. There are bacteria literally everywhere in the environment, and a few cause human diseases. Just as in sports where a scorecard is necessary to know the players, some knowledge of bacteria will help the reader, Humans—from the smallest children learning to talk to the astronomer studying craters on other planets—identify and name things So it is with microbiologists who study bacteria and biologists who study other forms of life. Everyone recognizes different mammals—humans, dogs, cats, rats, mice, etc.—and recognizes their unique and salient features if not their scientific *names—Homo sapiens, Canis familiaris, Felis catus, Rattus rattus, Mus muscus.* Such easy familiarity is not possible with organisms that cannot be seen, and everyone has to rely on scientists' identification and nomenclature to talk about bacteria.

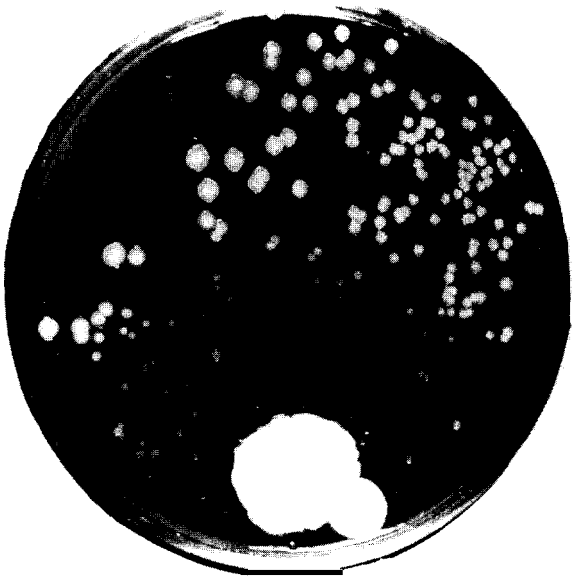
OTA associates bacteria with specific disease states, whenever possible, and uses standard scientific nomenclature. For example, the cause of cholera is *Vibrio cholerae,* where "Vibrio" is the name of a bacterial genus and "cholerae" is the name of a species. After the first use of such a name, the generic name is usually abbreviated, as in *V. cholerae.* When both generic and specific names are used, the words are italicized. When reference is made to a genus, such as "Enterococcus, " the name is capitalized but not italicized, The terms "different bacteria" or "several bacteria" refer to ill-defined collections of different genera. "Strains" refers to further divisions among a species; in particular, there are antibiotic-sensitive strains and antibiotic-resistant strains.



Reconstruction of Fleming's work bench in the room in which penicillin was discovered. St. Mary's Hospital Medical School, Paddington, London, England.

away to his laboratory at St. Mary's Hospital in London and looked at a number of Petri plates that he had seeded with bacteria. The plates had been incubated in his absence and the agar surfaces were sprinkled with colonies of Staphylococcus, a common bacterium frequently found on human skin. Dr. Fleming expected that outcome. One plate was different, however. In addition to the Staphylococcus, there was a large blue-green colony of a common mold called Penicillium. [There's nothing mysterious about the mold. Probably everyone has seen it on an orange that hid itself in the bottom of the refrigerator.] Fleming noted that the Staphylococcus colonies near the mold colony appeared to have dissolved (or "lysed," to use the technical term). He reasoned that the mold was producing and releasing an agent that killed and lysed the bacteria. He called the agent "penicillin." (While the Fleming discovery opened the door to the antibiotics era, there is some circumstantial evidence that people long ago may have benefited from antibiotics; see box 2-2.)

Almost a decade later, at Oxford, a group of researchers and engineers led by H.W. Florey accomplished what Fleming had been unable to do. They scaled up the production of penicillin so that the antibiotic was available in sufficient



Fleming's original culture plate showing fewer and lysed Staphylococcal colonies near the mold. St. Mary's Hospital Medical School, Paddington, London, England.



A production worker pouring penicillin-containing culture medium into a trough for collection in a milk can, mid-1940s. Photo courtesy of The National Museum of American History, Smithsonian Institution, Washington, DC,

BOX 2-2: Antibiotic Use by Ancient Civilizations?

Perhaps unknowingly, earlier civilizations may have benefited from antibiotics. Bassett, Keith, Armelagos, et al. (1980) found evidence for the antibiotic tetracycline in the bones of Nubians who had been buried between 350 and 550 A.D. Streptomycetes, the bacteria from which many antibiotics are derived, are common in the Nubian Sudanese desert, and it is to be expected that the bacteria would have been picked up when the Nubians harvested grain for bread and beer. Conditions in grain storage bins would have favored the growth of the Streptomycetes, which could have been the source of the antibiotic. Drawing upon other information, Bassett et al. state that infectious disease rates were low among this population of Nubians. Regardless of the details, this evidence indicates that humans have interacted with antibiotics from well before 1928.

SOURCE: E.J. Bassett, M.S. Keith, G.J. Armelagos, et al. 1980. "Tetracycline-labeled bone from ancient Sudanese Nubia." *Science* 209:1532-1534.

quantities to be released to the Armed Forces to treat wounded servicemen as well as those with diseases. Early production methods included growing hundreds of cultures of Penicillium in glass bottles (sometimes milk bottles were used), collecting the culture broth, and purifying, concentrating, and packaging the penicillin for shipment. The collection of the penicillin-containing culture medium could be done with devices as simple as a metal trough and a milk can. Currently, the growth (fermentation) of the organisms that produce penicillin and other antibiotics is done in automated factories and with much higher efficiencies than were possible in the 1940s.

By 1944, penicillin supplies were large enough that some of the antibiotic was released for civilian use, and the first antibiotic that could be ingested or injected without toxic side effects entered medical practice. The cover of this report is a reproduction of a 1944 advertisement for penicillin. Penicillin was not made a prescription drug until the 1950s, and, for about a decade, it was available directly to the public (Levy 1992, p. 9).

Other "wonder drugs" followed penicillin, and many dreaded infectious diseases became treatable; people were saved from death and from prolonged periods of disability. Tuberculosis sanatoriums closed because antibiotics were sufficient treatment; people with burns over large areas of their bodies, who would have died in earlier years, survived; childhood meningitis (infections of membranes around the brain or spinal cord), formerly a death sentence, was treatable; prolonged, dangerous, and only-sometimes-effective treatments for syphilis and gonorrhea were replaced by injection or ingestion of an antibiotic. According to Schlessinger (1993), the use of antibiotics, along with nutrition and health education, increased the median lifespan by eight years, from 62 to 70 years, between 1935 and 1955. (There has been little change in median lifespan since 1955.)

The Limits of Antibiotics

Antibiotics can fail to cure an illness because the bacteria are intrinsically **resistant** toward the drugs or because they acquire **resistance**. Resistance is a property of bacteria that confers the capacity to inactivate or exclude antibiotics or a mechanism that blocks the inhibitory or killing effects of antibiotics. Acquired resistance, hereafter simply "resistance," which is characterized by changes in bacteria such that organisms that were formerly treatable with an antibiotic become untreatable, is the focus of this report.

Most bacterial infections can be successfully treated with one antibiotic or another, but the emergence of resistance to older antibiotics, such as penicillin, leads physicians to prescribe newer antibiotics as the first choice in treating many diseases. The use of the newer antibiotic increases selective pressure for the emergence and spread of bacteria resistant to it, and the more an antibiotic is used, the greater the chance that resistance to it will emerge and spread.

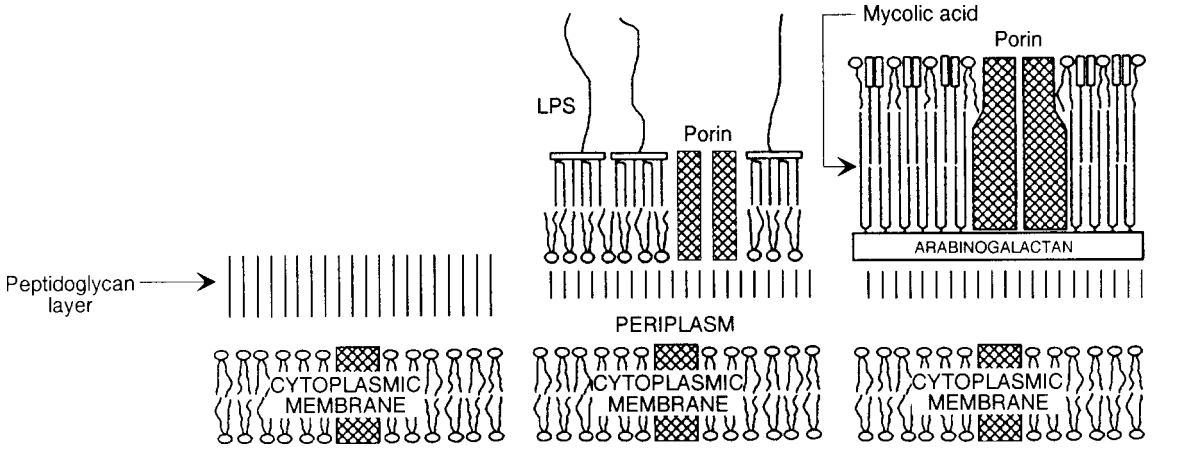
Before turning to the discussion of resistance, some other reasons for treatment failure will be mentioned.

Antibiotics are generally active only against bacteria and not against fungi, protozoa or viruses: Antibiotics act against physiological and biochemical pathways that are specific to bacteria. As already mentioned, antibiotics have few effects in animal and human cells that have biochemical pathways somewhat different from those of bacteria. Other microorganisms, such as fungi (e.g., yeast) and protozoa, also have biochemical pathways different from those of bacteria and, as a result, antibiotics will not work against them. Antibiotics have no effect on viruses because viruses do not have their own biochemistry; they use the biochemical machinery of their host cells that presents no targets for antibiotic action. Despite knowledge that antibiotics work only against bacterial infections, patients request—and physicians prescribe—antibiotics for viral infections, such as the common cold. The consequences of this "inappropriate use" or "overuse" are discussed in chapters 3 and 4.

Some antibiotics are active against only certain kinds of bacteria: There is great diversity among bacteria, and they do not share **all** of the same biochemical and physiological pathways. Therefore, not all antibiotics are active against all bacteria. For example, penicillin works by inhibiting the growth of the bacterial cell wall. Mycobacteria, which are the cause of tuberculosis, do not have the same cell wall structure as other bacteria (figure 2-4), and penicillin will not affect growth of mycobacteria because there is no target for its action.

Mycobacteria walls are a specific example of properties that render some bacteria intrinsically resistant to one or more antibiotics. As a more general example, bacteria are classified as either Gram positive or Gram negative on the basis of their capacity to be colored by a biological stain, and the cell walls of the Gram positives differ from those of the Gram negatives. Some antibiotics are effective against only Gram-positive bacteria, some are effective against only Gram-negative bacteria, and some, the "broad-spectrum antibiotics," are effective against both.

FIGURE 2-4: Cell Envelopes of Bacteria



(Left) Most of the Gram-positive bacteria are covered by a porous peptidoglycan layer, which does not exclude most antimicrobial agents. (Middle) Gram-negative bacteria are surrounded by the outer membrane, which functions as an efficient barrier against many antibiotics. **(Right)** Mycobacteria produce an unusual bilayer, which functions as an exceptionally efficient barrier

SOURCE: H Nikaido, 1994 "Prevention of drug access to bacterial targets: Permeability barriers and active efflux. " *Science* 264:383. Copyright 1994, American Association for the Advancement of Science.

Some bacteria are virulent and can kill quickly: A virulent strain of group A streptococcus causes a disease called toxic shock-like syndrome (TSLS) which killed Muppeteer Jim Henson. Because this strain and other virulent bacteria can "fell otherwise healthy people within hours of the onset of symptoms" (Wright, 1990), antibiotics have to be administered very early in order to defeat the infection.

Some bacteria grow in biofilms that cannot be easily penetrated by antibiotics: Biofilms are multilayer bacterial populations embedded in a film that is attached to some surface. Some examples of bacteria growing in biofilms are the plaque that causes tooth decay, films of *Pseudomonas aeruginosa* that infect lung tissue especially in cystic fibrosis patients, and films that grow on the surfaces of medical devices such as catheters (see chapter 6). Antibiotics often cannot penetrate biofilms; therefore, even though the antibiotic may be effective against the strain of the bacteria in the laboratory, the antibiotic may be ineffective against the infection.

Mechanisms for the Emergence and Spread of Resistance

When a new antibiotic is introduced, many bacteria are susceptible to it. Hughes and Datta (1983) demonstrated that bacteria preserved from 1917-1954 (the "pre-antibiotic" era) had little if any antibiotic resistance except intrinsic resistance. However, since the dawn of the antibiotic age, acquired resistance to every known antibiotic has been observed in one or more bacterial strains. This resistance sometimes arises in an individual patient during the course of treatment, but more often people are infected by resistant bacteria that are acquired from the community or the hospital environment.

Mutations

Antibiotic resistance arises through processes that involve mutations and selection. Mutations occur spontaneously in bacterial DNA that modify or eliminate a target for an antibiotic's action, or that cause changes in the bacteria surface so that the antibiotic is not taken up, or that cause the production of an enzyme that inactivates the antibiotic, or that cause the antibiotic to be excreted from the bacterial cell. These mutations happen in the absence of any exposure to antibiotics, but the presence of an antibiotic favors the growth of the bacteria that contain a mutation for resistance, or in the usual jargon, the antibiotic "selects for" the mutant bacteria. Weiner (1995 at pp. 257-262) discusses the origins of mutations to antibiotic resistance and the selection of those mutations in an evolutionary context.

Mutations are of three general kinds. **Point mutations** are "single letter" mistakes that occasionally occur in copying the DNA code, and they can cause a small change in an enzyme or structural protein. The other two kinds of mutations, **insertions** and **deletions**, generally have more far-reaching effects; they can completely eliminate an enzyme activity or destroy a structural protein. Mutations are passed on to future generations of bacteria, and the number of resistant bacteria can increase very rapidly. Under the most favorable conditions, some bacteria can duplicate every 20 minutes.

As shown on figure 2-2, bacterial DNA is present on "chromosomes" and "plasmids." Chromosomes usually contain all the genes necessary for the life of the bacteria, and some genes that confer resistance to antibiotics are found on the chromosome. Plasmids, smaller pieces of DNA that replicate separately from the chromosome, can also be present. They can and often do carry genes for antibiotic resistance, and, as discussed below, they can be transferred from bacterium to bacterium.

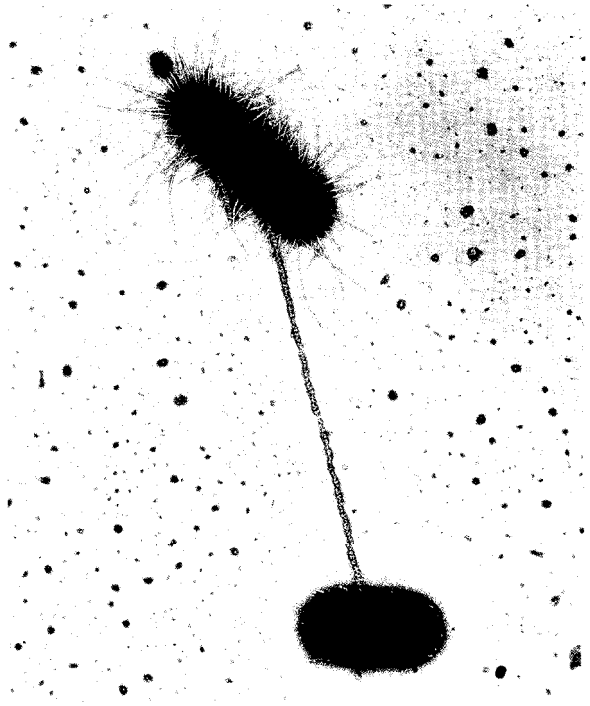
Chromosomal mutations

Genes for resistance to fluoroquinolone antibiotics (e.g., ciprofloxacin and ofloxacin) are known to occur, so far, only on chromosomes and not on plasmids. Single courses of therapy with fluoroquinolones may produce only low levels of resistance, but multiple mutations selected by repeated exposure to increasing doses of fluoroquinolones can confer high levels of resistance (Hooper and Wolfson, 1991). Even though muta-

tions occur only rarely, prolonged exposures to antibiotics can select for those mutations during a patient's treatment. In a study of 28 cystic fibrosis patients with chronic broncho-pulmonary *P. aeruginosa* infections treated with 14-day regimens of ciprofloxacin or ofloxacin, one developed resistance resulting in treatment failure, three developed intermediate resistance, and six developed low levels of resistance (Jensen et al., 1987). Three months after the end of treatment, the average resistance of the patients' *P. aeruginosa* to ciprofloxacin or ofloxacin remained somewhat higher than before treatment. Similarly, Chow et al. (1991) observed the development of antibiotic resistance in strains of Enterobacter during therapy.

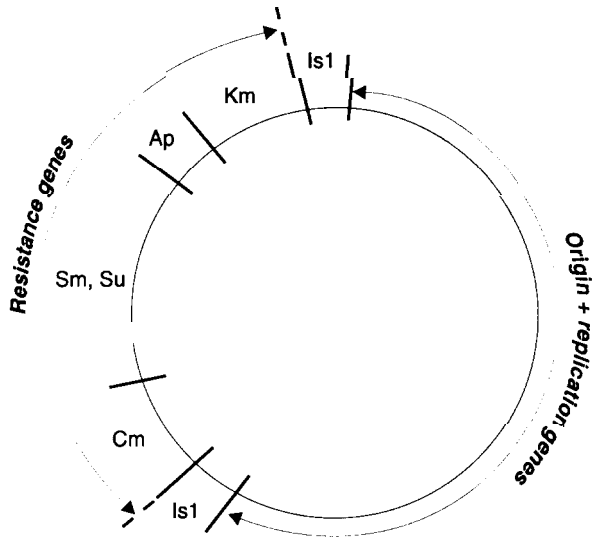
Plasmids and gene transfer

Plasmids are able to pass directly between bacteria through the process of **conjugation,** in which a newly replicated plasmid is transferred from the donor cell to the recipient cell through a pilus or conjugation tube. When the process is complete, both bacteria contain a copy of the plasmid, and both have the capacity to replicate and transfer the plasmid.



A Micrograph of conjugation between two bacteria. Photo courtesy of Dr. Charles Brinton, University of Pittsburgh.

FIGURE 2-5: Genetic Map of a Plasmid



Cm Chloramphenicol
Su Sulfonamide
Sm Streptomycin
Ap Ampicillin
Km Kanamycin
Is1 Transposon insertion factor

SOURCE: Office of Technology Assessment, 1995.

Plasmids can recombine with DNA from other plasmids, and that process can produce a single plasmid that carries multiple genes for resistance to different antibiotics (Condit and Levin 1990). This has important clinical consequences because the use of any one of the antibiotics shown in figure 2-5 could select for the plasmid that contains genes for resistance to all the antibiotics shown there.

Scientists confirmed the role of plasmids and conjugation in spreading antibiotic resistance during a dysentery epidemic in Japan in the late 1950s (Watanabe, 1963). The epidemic was characterized by increasing numbers of *Shigella dysenteriae* strains that were resistant to as many as four antibiotics simultaneously. Such bacteria became so frequent that health officials concluded that their emergence could not be attributed to repeated mutations arising in one bacterium after another because mutations occur

too rarely. Scientists showed that conjugational transfer of multiple-resistant plasmids accounted for the epidemic and established plasmids as major agents in the spread of antibiotic-resistant genes.

Hughes and Datta (1983), who examined preserved bacterial strains from the pre-antibiotic era, showed that plasmids were present in many of the bacteria and that 24 percent of the plasmids were able to be transferred by conjugation between bacteria. However, very few of the preserved bacteria were resistant to antibiotics and those few were resistant to only one antibiotic. This indicates that multi-resistance plasmids must have been created in the decades following the discovery of penicillin, when the use of antibiotics became extensive. Importantly, however, the pre-existing transferable plasmids in bacteria became the vehicle for transfer of multiple antibiotic-resistant genes.

Resistance genes can also travel on **transposons**, small pieces of DNA that can transfer to different sites on bacterial chromosomes and plasmids in the same bacterial cell or in different bacterial cells. Hall and coworkers (Hall and Stokes, 1993) have been studying the structure of some transposons called **integrons** that carry antibiotic-resistance genes. The integrons are like freight trains: sequences of DNA necessary for the functioning of the integrons at the front and the back are like the engine and the caboose, and any number of "cassettes" of resistance genes, like the cars of the train, can be carried between them. Different cassettes can insert into integrons, and this facilitates the acquisition of resistance genes by bacteria. Collis and Hall (1995) have also found that the **expression** of the integrons depends on their position in the cassette: resistance coded by genes close to the front of the train is stronger than resistance from genes near the back of the train. This helps explain the variability in the levels of resistance between different strains of bacteria.

The origin of the resistance genes that can be transferred between bacteria on plasmids and transposons is unknown, but some, at least, might have originated as a self-protective mechanism in antibiotic-producing organisms. For example, some strains of streptomyces that produce aminoglycosides (streptomycin is an aminoglycoside) also produce aminoglycoside-modifying enzymes (Benveniste and Davies, 1973).

Genes can be transferred between different species of bacteria. In a 1979 outbreak in a Kentucky hospital (Tauxe, Holmberg, and Cohen, 1989), 31 patients and personnel became infected with a strain of *Staph. aureus* that was resistant to methicillin, penicillin, gentamicin, erythromycin, clindamycin and tetracycline. Bacteria isolated from all of those affected contained the same resistance plasmid. Plasmids of a similar size were also found in the common skin commensal organism *Staph. epidermis* from the affected patients. Analysis of the plasmids by molecular techniques suggested that the same plasmid had been transferred between *Staph. aureus* and *Staph. epidermis*.

In another study that demonstrated inter-species transfer, Tauxe, Cavanagh, and Cohen (1989) examined multiple-antibiotic-resistant *E. coli* and *Shigella flexneri* that were isolated from a hospitalized patient. Their analysis indicated that the resistant genes had been transferred from the *E. coli* to the *S. flexneri* and that the antibiotic-resistant *S. flexneri* had then become the cause of a small outbreak of infections in the community. These examples show that resistance genes can be transferred between different bacterial species and demonstrate a pathway for widespread distribution of antibiotic-resistant genes.

There are two other mechanisms for gene transfer in addition to conjugation: **transduction** and **transformation**. In transduction, genes are transferred by bacterial viruses (called "bacteriophages" or "phages"). In transformation, pieces of DNA in the bacteria's environment are taken into the bacteria and incorporated into the bacterial chromosome. *Hemophilus influenzae* takes up DNA from its surroundings, and recently reported data indicate that transformation may play an important role in the survival of those bacteria (box 2-3).

BOX 2-3: The Complete DNA Sequence of *Haemophilus influenzae*

Using a variety of newly discovered methods, scientists have been working to sequence the DNA of several different organisms, from humans to mice to bacteria. These sequences, when complete, locate every "base" or "nucleotide," the chemical units that carry the genetic code in an organism's genome.

H.O. Smith and J.C. Venter led a group of scientists who completely mapped the DNA sequence of *Haemophilus influenzae* Rd (Fleischmann et al., 1995). Their success marked the first complete DNA sequence for any free-living organism, and Venter has announced that sequences for two other bacteria are nearly completed (Nowak, 1995).

The speed at which these sequences can be completed opens up a new era in understanding how bacterial DNA directs the activity of bacterial metabolism, and, in particular, it will enable scientists to understand the genes that are involved in virulence. For instance, *H. influenzae* Rb is a non-pathogenic "laboratory strain" which is closely related to the human pathogen *H. influenzae* b. By comparing the DNA sequences from the Rb and b strains of *H. influenzae*, Fleischmann and colleagues (1995) were able to demonstrate that eight genes that code for proteins necessary for the b strain to adhere to host cells were missing from the Rb strain. This suggests that the Rb strains may not be pathogenic, at least in part, because they cannot attach firmly to host cells.

H. influenzae can take up DNA from its environment and recombine the taken-up DNA into its own DNA through the process called transformation. Smith et al. (1995) found that certain DNA sequences occur at 1,465 different locations on the *H. influenzae* DNA and that these sequences cause the bacteria to preferentially take up and incorporate DNA from its own species.

This feature enhances the capacity of *H. influenzae* to take up DNA from other *H. influenzae* that have died. Why it would be desirable to take up DNA from bacteria that have been killed is unclear; presumably, the bacteria that die were less fit for their environment. However, the fact that the bacteria have so many recognition sequences suggests that the sequences, which increase opportunities for recombination between the DNA of the dead bacteria and the surviving bacteria, are of survival advantage to the bacteria.

SOURCES: R.D. Fleischmann, M.D. Adams, O. White, O., et al. 1995. " Whole-genome random sequencing and assembly of Haemophilus influenzae Rd." *Science* 269:496-512; Nowak, R. 1995. "Bacterial genome sequence bagged." *Science* 269:468-470; H.O. Smith, J.-F. Tomb, B.A. Dougherty, et al. 1995. "Frequency and distribution of DNA uptake signal sequences in the *Haemophilus influenzae* Rd genome." *Science* 269:538-540.

International Spread of Antibiotic Resistance

Antibiotic-resistance genes move with travelers from one country to another, making antibiotic resistance an international problem. O'Brien et al. (1985) document the intercontinental spread of an antibiotic-resistant gene on a plasmid, and Soares et al. (1992) reported the introduction of strains of multiple-resistant *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. These examples illustrate that antibiotic use and bacterial resistance patterns all over the world will have an impact on the United States and indicate the importance of international cooperation in dealing with the antibiotic-resistance problem.

Persistence of Antibiotic Resistance Genes in the Absence of Antibiotics

The extent to which antibiotic resistance can be controlled by limiting the use of antibiotics may be answered by studying the molecular mechanisms of transposon and plasmid replication and the behavior of populations of bacteria. Antibiotic use selects for bacteria that carry antibiotic-resistance genes, but the resistant bacteria might be less efficient or use more energy because they carry "excess baggage" of altered or extra genes.

Such genes can make the difference between survival and death in the presence of an antibiotic, but their maintenance in an antibiotic-free environment might put bacteria that bear them at a competitive disadvantage with bacteria that do not carry such genes.

Simonsen (1991) discusses the fate of plasmids in the absence of selection pressure from antibiotics. The "excess baggage" theory predicts that easing the selective pressure by decreasing the use of antibiotics would lead to a decrease in the carriage of antibiotic-resistance genes by bacteria. But Bouma and Lenski (1988) showed that this may not always be the case. They inserted a plasmid that carried a tetracycline-resistance gene into a strain of *E. coli*. The *E. coli* carrying the plasmid grew poorly as compared to *E. coli* without it (the plasmid is "excess baggage"). Of course, in the presence of tetracycline, the bacteria that did not have the plasmid would not grow. As expected, after 500 generations of growth in tetracycline, all bacteria contained the plasmid. Moreover, even in the absence of tetracycline, the plasmid-bearing bacteria now grew better than the bacteria without the plasmid. The bacteria had somehow adapted in those 500 generations to become more efficient while retaining the plasmid.

This result leads to the suggestion that evolution can produce plasmid-carrying bacteria that are not at significant disadvantage in competition with other bacteria in antibiotic-free environments. It can also be interpreted to indicate that plasmid-carrying bacteria will not be eliminated by eliminating antibiotics.

On the other hand, there are many examples in which controlling the use of antibiotics leads to a decrease in the frequency of bacteria carrying antibiotic-resistance genes. This may reflect that antibiotic-susceptible bacteria (those without "excess baggage") usually outgrow antibiotic-resistant bacteria so that the resistant bacteria become a smaller and smaller proportion of the total population. However, this process may be very slow, and the resistance does not decrease to zero. The observation that the antibiotic-resistant bacteria do not disappear (drop to zero) may be consistent with the results of Bouma and Lenski, because bacteria may adapt so that carrying plasmids containing resistance genes provides an advantage, even in the absence of the antibiotic.

CONFRONTING ANTIBIOTIC RESISTANCE

Currently, half a century after the introduction of "wonder drugs," scientists, physicians and the public fear the re-emergence of infectious diseases caused by antibiotic-resistant bacteria. Krause (1992) observed

> [M]icrobes are not idle bystanders, waiting for new opportunities offered by human mobility, ignorance or neglect. Microbes possess remarkable genetic versatility that enables them to develop new pathogenic vigor, to escape population immunity by acquiring new antigens, and to develop antibiotic resistance.

Scientists who contributed to the biological research that produced antibiotics warn that society has unwisely tolerated the risk that was evident in reports of the proliferation of genetic alterations in bacteria that spread antibiotic resistance:

> The stunning success of the pharmaceutical industry in the United States, Japan, the United Kingdom, France and Germany in creating new antibiotics over the past three decades has caused society and the scientific community to become complacent about the potential of bacterial resistance... [D]espite all these antibiotics, a person could die in a hospital in New York, San Francisco, Paris, Barcelona, Tokyo, or Singapore as a result of a resistant bacterial infection (Neu, 1992).

There are many questions surrounding antibiotic resistance. Is it possible that alternative strategies of scientific research and antibiotic development could have prevented this outcome? Have antibiotics been improperly prescribed or inappropriately requested by patients? If evidence was available from the start that disease-carrying bacteria could become resistant to antibiotics, what postponed the crisis for 50 years? Although the Institute of Medicine identified antibiotic-resistant microorganisms as only one of six factors contributing to the rising risk

of morbidity and mortality from infection, it warned that antibiotic resistance "may be a greater threat to the public than the emergence of a new disease" (IOM, 1992).

The following chapters discuss what is known about antibiotic resistance and address the important questions of what can be done now to help slow the emergence and spread of antibiotic-resistant bacteria, to preserve the capacity to treat bacterial infectious diseases with available antibiotics, and to develop new antibiotics.

REFERENCES

Benveniste, R., and J. Davies. 1973. Aminoglycoside antibiotic-inactivating enzymes in actinomycetes similar to those present in clinical isolates of antibiotic-resistant bacteria. *Proceedings of the National Academy of Science, U.S.A. 70*(8):2276–2280.

Bouma J.E., and R.E. Lenski. 1988. Evolution of a bacteria/plasmid association. *Nature 335*: 351–352.

Chow J.W., M.J. Fine, D.M. Shlaes, et al. 1991. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Annals of Internal Medicine 115*:585–590.

Collis, C.M., and R.M. Hall. 1995. Expression of antibiotic resistance genes in the integrated cassettes of integrons. *Antimicrobial Agents and Chemotherapy 39*:155–162.

Condit, R., and B.R. Levin. 1990. The evolution of plasmids carrying multiple resistance genes: the role of segregation, transposition, and homologous recombination. *The American Naturalist 135*:573–596.

Fleischmann, R.D., M.D. Adams, O. White, et al. 1995. Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. *Science 269*:496–512.

Hall, R.M., and H.W. Stokes. Integrons: novel DNA elements which capture genes by site-specific recombination. *Genetica 90*:115–132.

Holmberg, S.D., J.D. Wells, and M.L. Cohen. 1984. Animal-to-man transmission of antimicrobial-resistant *Salmonella:* investigations of U.S. outbreaks, 1971–1983. *Science 225*:833–835.

Hooper, D.C., and J.S. Wolfson. 1991. Fluoroquinolone antimicrobial agents. *New England Journal of Medicine 324*:384–394.

Hughes, V.M., and N. Datta. 1983. Conjugative plasmids in bacteria of the "pre-antibiotic" era. *Nature 302*:725–726.

Institute of Medicine. 1992. *Emerging Infections. Microbial Threats to Health in the United States*. Washington D.C. National Academy Press.

Jensen, T., S.S. Pedersen, C.H. Nielsen, et al. 1987. The efficacy and safety of ciprofloxacin and ofloxacin in chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. *Journal of Antimicrobial Chemotherapy 20*:585–594.

Krause, R.M. 1992. The origin of plagues: old and new. *Science 257*:1073–1082.

Levy, S. 1992. *The Antibiotic Paradox.* New York, NY. Plenum Press.

Neu, H.C. 1992. The crisis in antibiotic resistance. *Science 257*:1064–1073.

O'Brien, T.F., M. Del Pilar Pla, K.H. Mayer, et al. 1985. Intercontinental spread of a new antibiotic resistance gene on an epidemic plasmid. *Science 230*:87–88.

Schlessinger, D. 1993. Biological basis for antibacterial action. In: M. Schaechter, G. Medoff and B.I. Eisenstein (eds.) *Mechanisms of Microbial Disease: Second Edition* Baltimore, MD. Williams and Wilkins, pp. 77–89.

Simonsen, L. 1991. The existence conditions for bacterial plasmids: theory and reality. *Microbial Ecology 22*:187–205.

Smith, H.O., J.-F. Tomb, B.A. Dougherty, et al. 1995. Frequency and distribution of DNA uptake signal sequences in the *Haemophilus influenzae* Rd genome. *Science 269*:538–540.

Soares, S., K.G. Dristinsson, J.M. Musser, et al. 1992. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *Journal of Infectious Diseases 168*:158–163.

Spika, J.S., S.H. Waterman, G.W. Soo Hoo, et al. 1987. Chloramphenicol-resistant *Salmonella newport* traced through hamburger to dairy farms. *New England Journal of Medicine 316*:565–570.

Tauxe, R.V., T.R. Cavanagh, and M.L. Cohen. 1989. Interspecies gene transfer in vivo producing an outbreak of multiple resistant shigellosis. *The Journal of Infectious Diseases 160*:1066–1070.

Tauxe, R.V., S.D. Holmberg, and M.L. Cohen. 1989. The epidemiology of gene transfer in the environment. In: S.B. Levy and R.V. Miller (eds.) *Gene Transfer in the Environment*. New York, NY. McGraw-Hill Publishing Company, pp. 377–403.

Watanabe, T. 1963. Infective heredity of multidrug resistance in bacteria. *Bacteriological Reviews 27*:87–115.

Watson, J.D., N.H. Hopkins, J.W. Roberts, et al. 1986. *Molecular Biology of the Gene: Fourth Edition Vol. 1: General Principles*. Menlo Park, CA. Benjamin/Cummings Publishing Co., p 123.

Weiner, J. 1995. *The Beak of the Finch: A Story of Evolution in Our Time*. New York, NY. Alfred A. Knopf.

Wright, K. 1990. Bad news bacteria. *Science 249*:22–24.

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 bet-

ter 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-threat-

ening. 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 vom-

iting, 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 non-resistant 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**	
Brucellosis	**Leprosy (Hansen disease)**	Rubella
Chancroid*	**Leptospirosis**	**Salmonellosis***
Cholera	**Lyme disease**	**Shigellosis**
Congenital rubella syndrome	**Lymphogranuloma venereum***	**Syphilis**
Diphtheria	Malaria	**Syphilis, congenital**
DRSP**	Measles	Tetanus
Encephalitis	**Meningococcal infection**	**Toxic shock syndrome**
Escherichia coli O157:H7*	Mumps	Trichinosis
Gonorrhea	**Pertussis**	**TB**
Granuloma inguinale	**Plague**	**Tularemia**
Haemophilus influenzae	Poliomyelitis	**Typhoid fever**
	Psittacosis	Varicella (chicken pox) +*
		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.

REFERENCES

American Medical Association, Council on Scientific Affairs. 1993. Food Safety *Archives of Family Medicine 2*:210-214.

Anderson, G.M. Feb. 10, 1990. Sick behind bars: health care in prison. *America 134*:124-126.

Ballow, C.H., and Schentag, J.J. 1992. Trends in antibiotic utilization and bacterial resistance (Report of the National Nosocomial Resistance Surveillance Group). *Diagnostic Microbiology and Infectious Diseases 15*: 37S-42S.

Barry, M., Wall, C., Shirley, L., et al., 1986. TB screening in Boston's homeless shelters. *Public Health Reports 101*(5):487-494.

Bellin, E.Y., Fletcher, D.D., and Safyer, S.M. 1993. Association of tuberculosis infection with increased time in or admission to the New York City jail system. *Journal of the American Medical Association 269*(17): 2228-2231.

Berkelman, R.L., Bryan, R.T., Osterholm, M.T., et al., 1994. Infectious disease surveillance: A crumbling foundation. *Science 264*:368-370.

Besser, R.E., Lett, S.M., Weber, J.T., et al., 1993. An outbreak of diarrhea and hemolytic uremic syndrome from *Escherichia coli* O157:H7 in fresh-pressed apple cider. *Journal of the American Medical Association 269*(17):2217-2220.

Boodman, S.G. August 15, 1995. 45 Infected with TB by homeless man. *Washington Post*, Health section, p.11.

Breiman, R.F., Butler, J.C., Tenover, F.C., et al., 1994. Emergence of drug-resistant pneumococcal infections in the United States. *Journal of the American Medical Association 271*(23):1831-1835.

Cassell, G. June 22, 1995. Department of Microbiology, University of Alabama at Birmingham. Personal communication.

Chisolm, S.A. 1988. Infection control in correctional facilities: A new challenge. *American Journal of Infection Control 16*:107-113.

Cohen, D., Scribner, R., Clark, J., Cory, D. 1992. The potential role of custody facilities in controlling sexually transmitted diseases. *American Journal of Public Health 82*(4): 552-556.

Cohen, M.L., and R.V. Tauxe. 1986. Drug-resistant salmonella in the United States: An epidemiologic perspective. *Science 234*:964-969.

DiNubile, M.J. 1990. Antibiotics: The antipyretics of choice. *American Journal of Medicine 89*:787-788.

Fornasini, M., Reves, R., Murray, B., et al., 1992. Trimethoprim-resistant *Escherichia coli* in households of children attending day care centers. *Journal of Infectious Diseases 166*(2):326-330.

Frieden, T.R., Fujiwara, P.I., Washko, R.M., Hamburg, M.A. 1995. Tuberculosis in New York City—turning the tide. *The New England Journal of Medicine 333*(4):229-233.

Frieden, T.R., and R.J. Mangi. 1990. Inappropriate use of oral ciprofloxacin. *Journal of the American Medical Association 264*(11): 1438-1440.

Garrett, L. 1994. *The Coming Plague: Newly Emerging Diseases in a World Out of Balance* (New York, NY: Farrar, Straus, and Giroux).

Gray, G.C., Mitchell, B.S., Tueller, J.E., et al., 1994. Pneumonia hospitalizations in the U.S. Navy and Marine Corps: Rates and risk factors for 6,522 admissions, 1981-1991. *American Journal of Epidemiology 139*(8): 793-802.

Gross, T.P., and M.L. Rosenberg. 1987. Shelters for battered women and their children: an under-recognized source of communicable disease transmission. *American Journal of Public Health 77*(9):1198-1201.

Haglund, L.A., Istre, G.R., Pickett, D.A., et al., 1993. Invasive pneumococcal disease in central Oklahoma: Emergence of high-level penicillin resistance and multiple antibiotic resistance. *Journal of Infectious Diseases 168*(6):1532-1536.

Hammond, A. (ed.) 1994. *The 1994 Information Please Environmental Almanac* (New York, NY: Houghton Mifflin Co.).

Hatakka, M., and K. Asplund. 1993. The occurrence of salmonella in airline meals. *Acta Veterinaria Scandinavica 34*(4):391-396.

Hoge, C.W., Reichler, M.R., Dominguez, E.A., et al., 1994. An epidemic of pneumococcal disease in an overcrowded, inadequately ventilated jail. *The New England Journal of Medicine 331*(10):643-648.

Holmberg, S.D., Osterholm, M.T., Senger, K.A., Cohen, M.L. 1984. Drug-resistant salmonella from animals fed antimicrobials. *The New England Journal of Medicine 311*(10): 617-622.

Institute of Medicine. 1992. *Emerging Infections: Microbial Threats to Health in the United States*, J. Lederberg, R.E. Shope, and S.C.J. Oaks (eds.) (Washington, DC: National Academy Press).

Jernigan, D.B., Cetron, M.S., Breiman, R.F., et al., April 18, 1995. Centers for Disease Control and Prevention, Atlanta, GA. A national strategy for the surveillance, applied research, prevention, and control of drug-resistant *Streptococcus pneumoniae* (unpublished document).

Kim, J.H., and H.A. Gallis. 1989. Observations on spiraling empiricism: Its causes, allure, and perils, with particular reference to antibiotic therapy. *American Journal of Medicine 87*:201-206.

Klein, J.O. 1994. Otitis externa, otitis media, mastoiditis. In G.L. Mandell, J.E. Bennett, and R. Dolin (eds.) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases* (New York: Churchill Livingstone).

Klugman, K.P. 1990. Pneumococcal resistance to antibiotics. *Clinical Microbiology Reviews. 3*:171-196.

Kunin, C.M., Tupasi, C., Craig, W.A. 1973. Use of antibiotics: A brief exposition of the problem and some tentative solutions. *Annals of Internal Medicine 79*:555-560.

Kunin, C.M. 1995. Relationships between antibiotic use and the emergence and persistance of antibiotic resistance (unpublished paper).

Lee, L.A., Puhr, N.D., Maloney, E.K., et al., 1994. Increase in antimicrobial-resistant salmonella infections in the United States, 1989-1990. *The Journal of Infectious Diseases 170*:128-134.

Levine, D.P., Fromm, B.S., and Reddy, B.R. 1991. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Annals of Internal Medicine, 115*:674-680.

Levine, M. and O. Levine. 1995. Changes in human ecology and behavior in relation to the emergence of diarrheal diseases, including cholera. In B. Roizman (ed.) *Infectious Diseases in an Age of Change* (Washington, DC: National Academy Press).

Levy, S.B. 1992. *The antibiotic paradox: How miracle drugs are destroying the miracle* (New York: Plenum Press).

Madhavan, T. 1994. Infections in the elderly: Current concepts in management. *Comprehensive Therapy 20*(8):465-470.

Maurice, J. 1994. The rise and rise of food poisoning. *New Scientist 144*(1956):28-33.

McCaig, L.F. and J.M. Hughes. 1995. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *Journal of the American Medical Association 273*(3):214-219.

McGowan, J.E.J. 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Reviews of Infectious Diseases 5*(6):1033-1048.

Moller, J.K. 1989. Antimicrobial usage and microbial resistance in a university hospital during a seven-year period. *Journal of Antimicrobial Chemotherapy 24*:983-992.

Morris, J. and C. McAllister. 1992. Homeless individuals and drug-resistant tuberculosis in South Texas. *Chest 102*(3):802-804.

Morse, S. August 15, 1995. Centers for Disease Control and Prevention, National Center for Infectious Diseases, Atlanta, GA. personal communication.

Mouton, R.P., Herman, J., Simoons-Smit, A.M., et al., 1990. Correlations between consumption of antibiotics and methicillin resistance in coagulase negative staphylococci. *Journal of Antimicrobial Chemotherapy 26*:573-583.

Navarro, M. May 5, 1993. Report links time spent in jail to risk of tuberculosis. *New York Times*, p. B5.

Pablos-Mendes, A., Raviglione, M., Battan, R., et al., 1990. Drug-resistant TB among the homeless in N.Y.C. *N.Y. State Journal of Medicine 90*(7):351-355.

Paul, E.A., Lebowitz, S.M., Moore, R.E., et al., 1993. Nemesis revisited: Tuberculosis infection in a New York City men's shelter. *American Journal of Public Health 83*(12): 1743-1745.

Rauch, A., O'Ryan, M., Van, R., Pickering, L. 1990. Invasive disease due to multiply resistant *Streptococcus pneumoniae* in a Houston, Texas, day care center. *American Journal of Diseases in Children 144*(8):923-927.

Riley, L.W., Remis, R.S., Helgerson, S.D., et al., 1983. Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. *New England Journal of Medicine 308*:681-685.

Ringertz, S. and G. Kronvall. 1987. Increased use of erythromycin causes resistance in *Haemophilus influenzae*. *Scandinavian Journal of Infectious Diseases 19*:247-256.

Schappert, S.M. Sept. 1992. Office visits for otitis media: United States, 1975-90. *Advance Data From Vital and Health Statistics of the National Center for Health Statistics, No. 214* (PHS) 88-1250 (Hyattsville, MD).

Schlessinger, D. 1993. Biological basis for antibacterial action. In M. Schaechter, G. Medoff, and B.I. Eisenstein (eds.) *Mechanisms of Microbial Disease* (Baltimore, MD: Williams and Wilkins).

Schwarcz, S.K., Zenilman, J.M., Schnell, D., et al., 1990. National surveillance of antimicrobial resistance in *Neisseria gonorrhoeae*. *Journal of the American Medical Association 264*(11):1413-1417.

Skolnick, A.A. 1992. Some experts suggest the Nation's 'war on drugs' is helping. *Journal of the American Medical Association 268* (22):3177-3178.

Snydman, D. and S. Gorbach. 1982. Salmonellosis: Nontyphoidal. In A. Evans and H. Feldman (eds.) *Bacterial Infections of Humans* (New York, NY: Plenum Medical Book Co.).

Sogaard, H., Zimmerman-Nielsen, C., and Sibioni, K. 1974. Antibiotic resistant gram-negative bacilli in a urological ward. *Journal of Infectious Diseases 130*:646.

Sterne, G.G., Hinman, A., and Schmid, S. 1986. Potential health benefits of child day care attendance. *Reviews of Infectious Diseases 8*(4):660-662.

Swerdlow, D.L., Woodruff, B.A., Brady, R.C., et al., 1993. A waterborne outbreak in Missouri of *Escherichia coli* O157:H7 associated with bloody diarrhea and death. *Annals of Internal Medicine 117*(10):812-819.

Tan, T., Mason, Jr., E., and Kaplan, S. 1993. Penicillin-resistant systemic pneumococcal infections in children: A retrospective case-control study. *Pediatrics 92*(6):761-767.

Tauxe, R.V., Tormey, M.P., Mascola, L., et al., 1987. Salmonellosis outbreak on transatlantic flights; foodborne illness on aircraft: 1947-1984. *American Journal of Epidemiology 125*(1):150-157.

Thacker, S.B., Addiss, D.G., Goodman, R.A., Holloway, B. 1992. Infectious diseases and injuries in child day care. *Journal of the American Medical Association 268*(13): 1720-1726.

U.S. Congress, General Accounting Office, 1994. *Drinking water: Stronger efforts essential for small communities to comply with standards*. RCED-94-40 (Washington, DC: U.S. Government Printing Office).

U.S. Congress, Office of Technology Assessment. July 1987. *Life-Sustaining Technologies and the Elderly*. OTA-BA-306 (Washington, DC: U.S. Government Printing Office).

U.S. Congress, Office of Technology Assessment. Sept. 1992. *Does Health Insurance Make a Difference?* OTA-BP-H-89 (Washington, DC: U.S. Government Printing Office).

U.S. Congress, Office of Technology Assessment. Sept. 1993. *The Continuing Challenge of Tuberculosis.* OTA-H-574 (Washington, DC: U.S. Government Printing Office).

U.S. Department of Commerce, U.S. Bureau of Census. 1994. *Statistical Abstract of the United States* (Washington, DC: U.S. Government Printing Office).

Villarino, M., Vugia, D., Bean, N., et al., 1992. Foodborne disease prevention in health care facilities. In J. Bennett and P. Brachman (eds.) *Hospital Infections* (Boston, MA: Little, Brown and Company).

Wasserheit, J. 1995. Effect of human ecology and behavior on sexually transmitted diseases, including HIV infection. In B. Roizman (ed.) *Infectious Diseases in an Age of Change* (Washington, DC: National Academy Press).

Weissman, J.S., Stern, R., Fielding, S.L., Epstein, A.M. 1991. Delayed access to health care: Risk factors, reasons, and consequences. *Annals of Internal Medicine 114* (4):325-331.

Whitnack, E. 1993. Streptococci. In M. Schaechter, G. Medoff, and B. Eisenstein (eds.) *Mechanisms of Microbial Disease* (Baltimore, MD: Williams and Wilkins).

Williams, R.D. Dec. 1994. Protecting little pitchers. *FDA Consumer* 10-14.

Antibiotic Use in Hospitals 4

At any given time, 25 to 35 percent of hospitalized patients are receiving systemic antibiotics (Eickhoff, 1991) to treat active infections or to prevent potential infections. The heavy use of antibiotics in the hospital exerts enormous selective pressure for the emergence and spread of antibiotic-resistant bacteria. Consequently, many of the two million bacterial infections acquired in the hospital are antibiotic-resistant, and a few are resistant to every antibiotic currently approved for use. Some hospitals have reduced infections from antibiotic-resistant bacteria through a combination of infection control procedures that prevent the spread of the resistant organisms and through monitoring and control of antibiotic use.

This chapter 1) describes antibiotic use in hospitals and its contribution to the rise of antibiotic-resistant nosocomial infections, 2) discusses current efforts to control antibiotic-resistant infections, 3) explores medical and financial factors that make such efforts difficult to implement in hospitals, and 4) discusses some possible solutions.

INFECTIONS ACQUIRED IN THE HOSPITAL

The Centers for Disease Control and Prevention (CDC) estimates that 1 out of 20 patients (2 million per year) acquire infections in the hospital (Haley et al., 1985).[1] Nosocomial infections cost $4.5 billion a year (1992 dollars) in terms of extra treatment and days of hospitalization, directly cause 19,000 deaths, and contribute to 58,000 deaths annually (table 4-1). The 19,000 deaths per year directly caused by nosocomial infections makes them the 11th leading cause of death in the U.S. population (Martone et al., 1992).

Recent data from the National Nosocomial Infections Surveillance (NNIS) system show that nosocomial infections are increasing (figure 4-1). The number of blood stream infections increased 279 percent in small non-teaching hospitals, 196 percent in large non-teaching hospitals, by 124 percent in small teaching hospitals, and by 70 percent in large teaching hospitals during the 1980s. It might be discouraging that the rates of blood stream infections have been increasing

[1] Based on data from CDC's 1976 Study on the Efficacy of Nosocomial Infection Control (SENIC). This number is still widely quoted in recent reports (see, for example, IOM, 1992).

	Extra days		Extra charges		Deaths directly caused by infections	Deaths to which infections contributed
	Avg. per infection[a]	Est. U.S. total[b]	Avg. extra charges per infection in 1992 dollars[c]	Est. U.S. total in 1992 dollars[b]	Est. U.S. total[b]	Est. U.S. total[b]
Surgical wound infection	7.3	3,726,000	$3,152	$1,609,000,000	3,251	9,726
Pneumonia	5.9	1,339,000	$5,683	$1,290,000,000	7,087	22,983
Bacteremia	7.4	762,000	$3,517	$362,000,000	4,496	8,844
Urinary tract infection	1.0	903,000	$680	$615,000,000	947	6,503
Other site	4.8	1,946,000	$1,617	$656,000,000	3,246	10,036
All sites	4.0[d]	8,676,000	$2,100	$4,532,000,000	19,027	58,092

[a] Adapted from R.W. Haley et al., Extra days and prolongation of stay attributable to nosocomial infections: A prospective interhospital comparison. *American Journal of Medicine* 70:51, 1981, by pooling data from the three SENIC pilot study hospitals.

[b] Estimated by multiplying the total number of nosocomial infections estimated in the SENIC Project (R.W. Haley et al., The nation-wide nosocomial infection rate: A new need for vital statistics. *American Journal of Epidemiology* 121:159, 1985) by the average extra days, average extra charges, or percentage of infections causing or contributing to death, respectively.

[c] 1992 dollars estimated from R.W. Haley et al., *Amer. J. Med.* 70:51, 1981, by pooling data from the three hospitals and adjusting for the annual rate of inflation of hospital expenses from 1976 to 1992 (range 5.0 to 12.3 percent) obtained from the American Hospital Association's National Panel Survey. Estimates for inflation rates in 1991 and 1992 were projected from 1987 to 1990 trend.

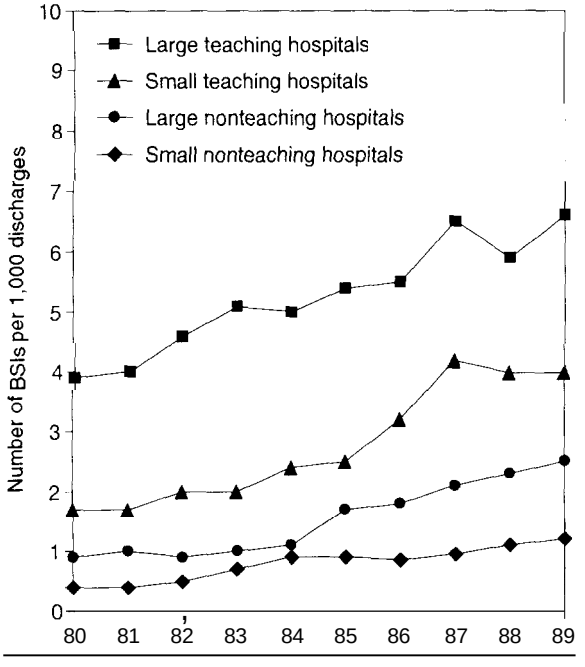
[d] Nationwide estimate obtained by summing the products of the site-specific estimate of the average extra days, average extra charges, or the percentage of infections causing or contributing to death, respectively, from the SENIC pilot studies (R.W. Haley et al., *Amer. J. Med.* 70:51, 1981), and the nationwide estimate of the proportion of nosocomial infections affecting the site from the main SENIC analysis (R.W. Haley et al., *Amer. J. Epidemiol.* 121:159, 1985).

SOURCE: W.J. Martone, W.R. Jarvis, D.H. Culver, et al. 1992. Incidence and nature of endemic and epidemic nosocomial infections. In: J.V. Bennett and P.S. Brackman (eds.) *Hospital Infections* Third edition. Boston, MA. Little, Brown and Company, pp. 593.

despite guidelines developed by CDC and the adoption of "universal precautions" to control infections. However, these increasing rates are partially due to recent advances in medicine. Increasing rates of surgery and catheterization provide opportunities for bacteria to penetrate into the body where they can cause infections. In addition, tissue and organ transplants, which are becoming more frequent and successful, require immunosuppression so that the foreign tissue is not rejected by the transplant recipient. Consequently, immunosuppressed patients are dependent on antibiotics to control bacterial infections.

Treatment with an antibiotic may suppress enough normal microbial flora (commensals) to leave a patient susceptible to infection by other organisms—especially antibiotic-resistant bacteria-unaffected by the antibiotic. Kollef (1 994) cites studies that show intensive care unit patients who had received antibiotics were more likely to develop ventilator-associated pneumonia caused by virulent species such as *Pseudomonas aeruginosa* or Acinetobacter, and that patients with those infections were almost twice as likely to die from them as patients infected with less virulent species.

FIGURE 4-1: Bloodstream Infection (BSI) Rates for All Pathogens in Various Types of Hospitals



SOURCE: S.N. Banerjee, T.G. Emori, D.H. Culver, et al, 1991. *American Journal of Medicine 91* (Suppl. 3B):86S-89S

THE RISE OF ANTIBIOTIC-RESISTANT INFECTIONS IN HOSPITALS

CDC operates the NNIS system that gathers voluntary information from approximately 200 hospitals, and through NNIS, CDC has documented increases in the number of nosocomial infections caused by antibiotic-resistant bacteria. Two important cases are the increasing numbers of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). Resistant strains of Klebsiella, Pseudomonas, *Escherichia coli,* and coagulase-negative Staphylococci also cause serious problems in hospitals.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Nosocomial *Staphylococcus aureus* infections have been a recurrent problem in hospitals for many years. This is partially due to the high rate of colonization in the population: about 50 percent of the population are intermittent carriers of *Staph. aureus,* and about 30 percent of the population are prolonged carriers of the bacteria in their nostrils or on their skin (Waldvogel, 1995). When these colonizing organisms enter internal organs of the body through invasive surgery, catheterizations, or other hospital procedures, they can cause infection. Strains resistant to penicillin were identified soon after its introduction (Spink and Ferris, 1945). Currently, more than 90 percent of all *Staph. aureus* are resistant to penicillin (Mandell and Sande, 1990). These strains of staphylococci were most likely resistant through the production of beta -lactamases that destroy penicillin and penicillin-like antibiotics.

The synthetic penicillin, methicillin, introduced in 1960, is not affected by many beta-lactamases. However, strains of staphylococci that

contain a chromosomal gene called *mec A* which encodes a modified penicillin-binding protein have been identified. These strains, commonly referred to as MRSA, are resistant to all beta-lactam antibiotics, and frequently also contain plasmid-encoded genes for resistance to other antibiotics (see chapter 2). MRSA were initially susceptible to the fluoroquinolones introduced in the 1980s, such as ciprofloxacin, but they quickly became resistant to these antibiotics. NNIS data document the increase in MRSA (figure 4-2). By 1992, more than 40 percent of *Staph. aureus* infections in large hospitals were methicillin-resistant. Some strains of MRSA are resistant to all antibiotics currently approved by the U.S. Food and Drug Administration (FDA), with the exception of vancomycin; others are susceptible to other antibiotics as well as vancomycin (see chapter 5).

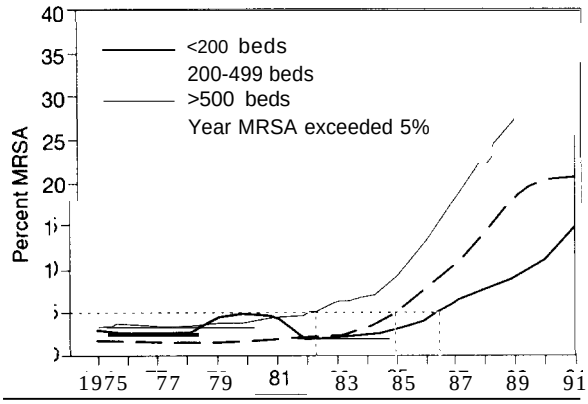
▮ Vancomycin-Resistant Enterococcus

Some strains of Enterococcus are resistant to ***all*** available antibiotics approved by FDA, and they are, therefore, untreatable with antibiotics. NNIS data showing the increase in VRE are presented in figure 4-3. As of 1994, almost 13 percent of enterococci acquired in intensive care units (ICUs) were resistant to vancomycin, and about 8 percent of enterococci acquired outside of ICUs were resistant. There is currently no FDA-approved antibiotic to treat many of these infections.[2]

▮ Vancomycin-Resistant MRSA?

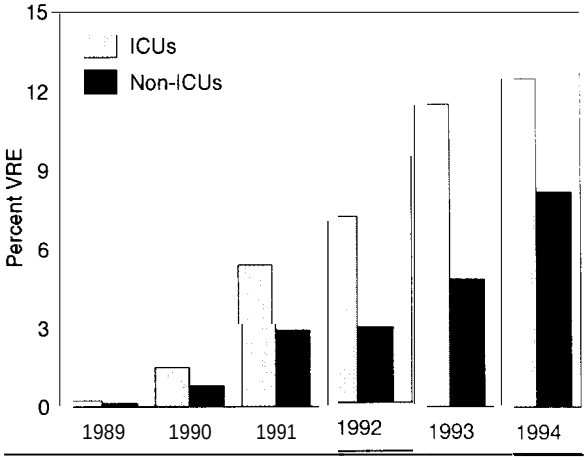
A huge fear among clinicians and epidemiologists is the possibility of the emergence of vancomycin-resistant strains of MRSA that are both highly virulent and untreatable. As this report goes to press, no confirmed vancomycin-resistant strain of MRSA has been reported to public health officials at CDC or elsewhere. However, Noble, Virani, and Cree (1992) demonstrated the transfer of a vancomycin resistance gene from an Enterococcus to *Staph. aureus* in the laboratory, indicating that the clinical emergence of vanco-

FIGURE 4-2: Methicillin-Resistant *Staphylococcus aureus* (MRSA) as a Percent of All *Staphylococcus aureus* in Hospitals of Different Sizes



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA

FIGURE 4-3: Vancomycin-Resistant Enterococcus (VRE) as a Percent of All Enterococcus in Intensive Care Units (ICUs) and Non-ICUs



SOURCE: National Nosocomial Infections Surveillance System Centers for Disease Control, Atlanta, GA.

[2] **Chapter 5 describes two new drugs, quinupristin/dalfopristin and teicoplanin, currently in clinical trials that may have activity against some strains of VRE, These drugs are available from the manufacturers on a compassionate-use basis to patients with VRE infections (The *Medical Letter on Drugs and Therapeutics,* 1994, at p. 31).**

mycin-resistant MRSA is possible. The only treatment available for some strains of MRSA is vancomycin, and the emergence of vancomycin-resistant MRSA may be inevitable. It will present a crisis in treatment.

THE USES OF ANTIBIOTICS IN HOSPITALS

Prophylactic Use of Antibiotics

In large surgical hospitals, half of all antibiotics are used to prevent possible infections (prophylaxis) (Kernodle and Kaiser, 1990). More than 30 years ago, Burke (1961) showed that prophylactic use of antibiotics before surgery reduces postoperative infection rates. Classen et al. (1992) investigated the timing of administration of antibiotics for prophylaxis and confirmed that antibiotics can prevent infections when administered two hours prior to surgery. They also suggested that antibiotics given at times other than in the 2 hours before surgery (one-third of all prophylactic antibiotics were given earlier than 2 hours before surgery or after surgery in this study of 2,847 patients) are not as effective in preventing infections (see table 4-2). Approximately 12 percent of the patients received antibiotics more than 2 hours before surgery; and more than 70 percent of the antibiotics given had half-lives ranging from 0.7–1.9 hours (Wenzel, 1992), suggesting that these antibiotics washed out of the patients' system before surgery began. In these cases it is clear that the use of antibiotics was inappropriate and that appropriate use of antibiotics would reduce the rate of infections and their associated costs because of decreases in the number of days that a patient is hospitalized. Moreover, appropriate use would reduce antibiotic use and help control antibiotic resistance.

Studies raise questions about the effects of prophylactic antibiotic use other than to prevent surgical wound infections. Kollef (1994a) found that prophylactic use of antibiotics for selective digestive decontamination designed to reduce nosocomial pneumonia reduced the incidence of pneumonia, but it had no effect on mortality. Apparently this phenomenon occurred because antibiotic-resistant bacteria that colonized some patients following the prophylactic treatment were harder to treat.

Classen et al. (1992) reported that more than 50 percent of the nosocomial infections they

TABLE 4-2: Temporal Relation between the Administration of Prophylactic Antibiotics and Rates of Surgical-Wound Infection

Time of administration*	No. of patients	No. (%) of infections	Relative risk (95% CI)	Odds ratio** (95% CI)
Early	369	14 (3.8)‡	6.7 (2.9–14.7)	4.3[a] (1.8–10.4)
Preoperative	1708	10 (0.59)	1.0	
Perioperative	282	4 (1.4)[b]	2.4 (0.9–7.9)	2.1[c] (0.6–7.4)
Postoperative	488	16 (3.3)‡	5.8‡ (2.6–12.3)	5.8[d] (2.4–13.8)
All	2847	44 (1.5)	————————	————————

* For the administration of antibiotics, "early" denotes 2 to 24 hours before the incision, "preoperative" 0 to 2 hours before the incision, "perioperative" within 3 hours after the incision, and "postoperative" more than 3 hours after the incision.

** As determined by logistic-regression analysis.

‡ P<0.0001 as compared with preoperative group (all P values were determined by logistic-regression analysis).

[a] P = 0.001.

[b] P = 0.12 as compared with preoperative group.

[c] P = 0.23.

[d] P = 0.0001.

SOURCE: C. Classen, R.S. Evans, S.L. Pestotnik, et al. 1992. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *New England Journal of Medicine* 326(5):283.

studied were caused by organisms resistant to the antibiotic used. In these cases the infections may have been caused because the resistant organisms were able to multiply when the susceptible normal bacterial flora of the patients was inhibited by the prophylactic antibiotics. Siegel et al. (1980) reported an especially tragic example of prophylactic use gone awry based on examination of the results of giving a single dose of penicillin to ward off streptococcal infections in some 9,000 newborns. Although penicillin-sensitive infections were reduced by the prophylactic treatment, infections with penicillin-resistant bacteria were more frequent in the babies who received the antibiotic, and mortality was higher from the resistant infections (15 of 35) than from the sensitive infections (3 of 27). Overall, the death rate from streptococcus infections was 3 times higher in the babies that received penicillin (1.2/1,000 vs. 0.43/1,000 live births).

Antibiotic Use to Treat Active Infections

The remainder of antibiotic use in hospitals is for treatment of active infections. It takes at least two days to identify the bacteria causing an infection and to determine its antibiotic susceptibility (see chapter 6). Therefore, the physician often has to make an empirical judgment about the identity of the bacteria and prescribe an antibiotic before the laboratory test results are available. If a patient is very sick, the physician will often use multiple antibiotics. If the patient is improving when the laboratory tests arrive, the physician might ignore the results of the tests and continue the patient on the empiric antibiotics. It is difficult to determine inappropriate antibiotic use and how to improve use in such cases.

The appearance of unexpected resistant organisms in one patient may influence a physician to routinely prescribe newer or broader spectrum antibiotics. A letter to the editor of the *New England Journal of Medicine* (Lonks et al., 1995) illustrates a case where a patient suffered because he was infected with an unlikely resistant strain. Physicians knew that no highly resistant strains of pneumococci had been reported in Providence, Rhode Island; only 2.3 percent of isolates obtained in hospitals in 1990 and 1991 showed intermediate-level resistance to penicillin, and none was highly resistant. An otherwise healthy 33-year-old man, who lived a little more than 30 miles from the city, was treated in the hospital for a *Streptococcus pneumoniae* infection. Assuming that the strain was not ceftriaxone-resistant, doctors treated the patient with dexamethasone and ceftriaxone for the first four days. After initial improvement, encephalitis developed, and doctors switched drugs to vancomycin and rifampin based on antibiotic-susceptibility test results that showed the infecting strains were resistant to penicillin and ceftriaxone. The patient's condition eventually improved and he was sent home. Based on this experience, the authors concluded that "*all patients* with the presumptive diagnosis of pneumococcal meningitis should receive high-dose ceftriaxone (or cefotaxime) plus vancomycin, with or without rifampin, until the isolate is proved to be susceptible to penicillin or ceftriaxone" [emphasis added]. It may be true that following this advice will prevent a few adverse outcomes such as those described in the letter to the journal. However, if similar reasoning is applied in many cases, the widespread use of antibiotics such as vancomycin will increase the risk for the emergence of antibiotic-resistant organisms.

In a study of the reasoning strategies used by physicians in empiric antibiotic selection, Yu et al. (1991) found that unexpected organisms appeared in 3.8 percent of all blood cultures. In these cases, antibiotics had been prescribed which were not the antibiotics of choice based on logical reasoning, but which did cover the unexpected organisms. The authors comment that "[t]hese memorable situations may have a disproportionate influence in these physicians' future selection of antibiotic therapy." They further conclude that "our disturbing and unexpected finding is that reflex prescription of broad-spectrum antibiotic therapy that is so often decried by academicians may have a rational basis" and that "educational efforts that emphasize narrow, rather than broad-spectrum prescribing may be inadequate to change physician prescribing habits."

LEGAL ASPECTS OF ANTIBIOTIC USE

Malpractice concerns might provide an additional incentive to prescribe antibiotics. According to data published by St. Paul Fire and Marine Insurance Company, a large nationwide malpractice insurer, a significant number of claims are related to infection-related illnesses and antibiotic use (St. Paul Fire and Marine Insurance Co., 1995). It is reasonable to speculate that fear of malpractice litigation may contribute to prescription of overly broad spectrum antibiotics or of antibiotics in cases where the chance of a bacterial infection is small. Box 4-1 contains excerpts from a commentary in the medical journal *Lancet* discussing the medical and legal controversy over the use of prophylactic antibiotics to prevent neonatal bacterial sepsis caused by Group B streptococcus.

BOX 4-1: Group B Streptococcus: The Controversy

Group B streptococcus (GBS) is the leading cause of neonatal bacterial sepsis in the United States, infecting about 12,000 newborns annually. Some newborns infected with GBS may die or have permanent neurological damage from meningitis. In 1992, both the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) issued protocols regarding the screening of pregnant women to detect and treat carriers of GBS in an effort to prevent neonatal GBS sepsis.

AAP called for universal prenatal GBS screening for all pregnant women at 26–28 weeks' gestation. Because certain population groups are more likely to carry GBS, ACOG advocated for optional screening targeted to certain populations where the incidence of neonatal GBS infection is inordinately high, such as populations where sexually transmitted diseases are common.

Inasmuch as GBS is part of the normal gut flora of some women and may or may not become a pathogen during pregnancy, both AAP and ACOG recommended intrapartum (during delivery) antibiotic treatment only to women with positive cultures who have additional high-risk factors such as preterm labor or premature rupture of the membranes before 37 weeks' gestation, fever in labor, multiple births, rupture of membranes for more than 18 hours at any gestational age, or a previous affected child.

The AAP and ACOG protocols leave a number of issues unresolved that expose obstetricians, family practitioners, and nurse midwives to considerable medicolegal liability. Screening for GBS during pregnancy does not provide certainty as to whether or not intrapartum antibiotic treatment is warranted. A study found that in women who were culture-positive at 28 weeks' gestation, 30 to 50 percent were culture-negative at the time of delivery; in women who were culture-negative at 28 weeks, 8 to 15 percent were culture-positive at the time of delivery. Consequently, some women will be treated unnecessarily and some who need treatment will be ignored.

Moreover, if only certain groups are targeted for screening in keeping with ACOG's protocol, can excluded groups hold health care professionals responsible if their newborn babies developed undetected GBS sepsis? Further, would the withholding of treatment in a pregnant woman with a positive culture who has no additional risk factors absolve a health care professional from medicolegal liability if that baby were affected?

The best approach to the management of GBS sepsis would be a rapid screening test during labor to determine whether antibiotic therapy is warranted, but the poor sensitivity of such tests currently renders them clinically useless. Until these tests are improved, health care professionals will most likely err on the side of caution and prescribe antibiotics even in extremely low-risk cases.

SOURCE: C.V. Towers, 1995, *Lancet* 346:197–198.

The following review of some malpractice suits exemplifies the dramatic consequences that can occur due to undertreating with antibiotics. In *Hellwig v. Potluri* (Case No. WL 285712, Ohio Court of Appeals 7th Circuit, 1991), the defendant emergency room physician was held liable for failing to prescribe antibiotics for the plaintiff who had stepped on a rusty nail at his home. The plaintiff developed osteomyelitis which forced him to "wear an appliance in his shoe and have an altered gait for the rest of his life." In *Toler v. United States of America* a plaintiff claimed that failure of a Veterans Administration (VA) hospital to administer an adequate course of antibiotics resulted in sepsis and death. In *Griffith v. West Suburban Hospital* (Case No. 86L-23904, Cook County, Illinois Circuit Court, 1993), a jury returned a $3.5-million verdict for failure to diagnose and timely treat a Group B Strep infection. In this case, a patient showed signs of respiratory distress shortly after birth, and although he was moved to an intensive care crib, antibiotics were not administered. Seven hours later, after being transferred to another hospital which then administered antibiotics, the patient died.

The medical and financial consequences of failing to prescribe prophylactic antibiotics for endocarditis can be considerable. In 1993, a dentist was held liable in *Orbay v. Castellanos* (Case No. 91-36124, Dade County Circuit Court, Miami, Florida, 1993) for failing to prescribe prophylactic antibiotics prior to tooth extraction. Soon after the tooth extraction, the plaintiff was diagnosed with bacterial endocarditis and underwent open heart valve replacement surgery. The defendant was held liable for failure to prescribe prophylactic antibiotics and failure to obtain a full medical history or medical clearance for a patient at risk of developing bacterial endocarditis. The jury awarded the plaintiff $1.24 million, which was reduced to $964,000 to reflect the decision that the plaintiff was 20 percent comparatively negligent for failure to take appropriate care of himself. However, a standard medical textbook comments:

> The issue of professional liability in the prophylaxis of endocarditis often has led to allegations of negligence and malpractice suits. . . . [It is hard] to prove that the failure of a physician or dentist to administer antibiotics was the direct cause of a patient acquiring endocarditis. If a strict demonstration of proximate cause were always required, it is doubtful that any claim based on the failure to administer prophylaxis could succeed, but juries are sometimes capricious in deciding liability in malpractice cases. . . (Mandell et al., 1990).

The "capricious" nature of the juries might bias physicians in favor of prescribing antibiotics, even when the risk of endocarditis (or other disease) is very minimal.

CONTROLLING THE EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE IN HOSPITALS

Part of the difficulty in controlling antibiotic resistance in hospitals is incomplete understanding of all the factors that contribute to the emergence and spread of antibiotic resistance in general. Most hospital personnel would agree that infection control is critical, but there are many disagreements about the benefits vs. cost of various infection control procedures. Few, if any, scientists disagree that the use of antibiotics is related to the emergence and spread of antibiotic resistance. Nevertheless, there are many controversies about how to implement programs to control the use of antibiotics.

Infection Control in Hospitals

In 1847, Ignac Semmelweis noticed that the rate of childbed fever in new mothers was much higher when the babies were delivered by obstetricians and medical students than by midwives and midwifery students. Semmelweis surmised that the high rate was due to the transmission of infectious particles from cadavers by the obstetricians and medical students and instituted the measure of handwashing in a chlorine solution. This measure greatly decreased the incidence of childbed fever (reviewed by Sanford, 1992).

In hospitals today, infection control procedures are considered absolutely essential. In 1976, CDC conducted a comprehensive Study on the Efficacy of Nosocomial Infection Control (SENIC) that measured the extent and effectiveness of infection control procedures in U.S. hospitals. The SENIC study included a survey of all hospitals in the United States and detailed interviews with representative hospitals. Twenty years later, the study remains the most comprehensive survey of the effectiveness of infection control procedures.[3] The study concluded that hospitals with intensive infection surveillance and control programs were able to reduce the rate of nosocomial infections by 32 percent (Haley et al., 1985). Yet the study found that only about 0.2 percent of U.S. hospitals had programs that effectively controlled all four of the major types of infections: surgical wound infection, urinary tract infection, primary bloodstream infection, and lower respiratory tract infection.

Infection Control Activities

The SENIC study concluded that a successful infection control program required leadership by a trained infection control physician, an infection control nurse for every 250 beds, organized infection surveillance efforts, and a system for reporting infection rates to practicing surgeons.

Handwashing and Other Precautions

Simple infection control procedures, such as handwashing and wearing gloves, reduce the spread of infections in hospitals, lowering the need for antibiotics and thereby reducing selective pressure for the spread of antibiotic-resistant bacteria. Health care workers have a large incentive to follow procedures such as universal precautions[4] because they were designed to protect them from infection from organisms such as the human immunodeficiency virus (HIV). However, in the hospital setting health care workers who respond to a life-threatening emergency often do not have time to put on gloves and follow proper infection control procedures. Willy et al. (1990) found that health care workers' perception of their own risk and potential spread of infections to patients is surprisingly low. In an anonymous nationwide survey of health care workers who might have frequent exposure to blood and other bodily fluids, only 55 percent of those responding reported routinely practicing universal precautions.

Human nature seems to prevent the full implementation of one of the simplest, yet most effective infection control method: handwashing. Handwashing is a proven method for reducing nosocomial infections, but the practice is not strictly followed. Handwashing compliance rates of less than 50 percent were observed in two studies of intensive care units (Simmons et al., 1990; Doebbeling et al., 1992). Goldmann and Larson (1992) make the following comments about the lack of compliance with handwashing:

> Experts in infection control coax, cajole, threaten, and plead, but still their colleagues neglect to wash their hands.... Education and persuasion do not generally lead to sustained improvement in handwashing. Physicians have been particularly refractory. Innovative approaches are needed desperately, but few have emerged.... There is so little confidence in hand-washing habits that hospital isolation policies now assume noncompliance.... [Original references not included].

Simmons et al. (1990) revealed one clue to handwashing noncompliance: nurses who were questioned about their handwashing practices believed they were washing their hands nearly

[3] SENIC data have the serious shortcoming that they were collected before implementation of current infection control procedures such as universal precautions, which were instituted beginning in 1985 largely because of the fear of transmission of the human immunodeficiency virus (HIV).

[4] Universal precautions include requirements that gloves be worn when handling bodily fluids, that needles and other sharp objects be disposed of in special containers to help prevent needle-stick accidents, and that health care workers with open or infected wounds have restricted contact with patients or patient care equipment (Garner, 1993).

90 percent of the time, when actual rates were between 22 and 29 percent.

Research into the seemingly simple question of which soap to use for washing hands may be useful in helping to prevent infections. Several studies have shown that a 7- to 10-second handwash with a non-antibacterial soap *increased* the transmission of bacteria due to the shedding of bacteria-laden skin cells, but that handwashing with antiseptic soaps reduces the rates of nosocomial infections (Martin, 1994). Rotter (1988) compared the efficacy of different antiseptics for washing hands and found that antiseptics containing isopropanol alcohol were significantly better at reducing skin bacteria than liquid soap.

Applying Infection Control Procedures to Control Antibiotic-Resistant Bacteria: Some Case Studies

Box 4-2 describes the successful countrywide control of MRSA in Denmark. The following case studies describe attempts to apply infection control procedures to control MRSA in nursing homes and hospitals in the United States.

Case 1: Successful control in a (mostly chronic care) VA medical center (Murray-Leisure et al., 1990)

The Lebanon, Pennsylvania, Medical Center is an 884-bed facility which successfully controlled an epidemic of MRSA patients during 1988–1989 within six months of instituting aggressive interventions. These interventions included confining known active MRSA carriers and MRSA-infected patients to one nursing unit, screening patients transferred into the facility for MRSA, using gown and glove isolation and treating both colonized and actively infected patients with topical and enteral antibiotics.

Case 2: Unsuccessful control in a VA medical center (Strausbaugh et al., 1992)

The Portland, Oregon, VA Medical Center Nursing Home Care Unit (NHCU) is a 120-bed facility that attempted to control MRSA primarily through administration of the antibiotics rifampin, trimethoprim-sulfamethoxazole, and clindamycin, used either alone or in different combinations, to asymptomatic carriers of MRSA. Other measures included restricting MRSA-infected or colonized patients to a small cluster of rooms, glove use to prevent the spread of any body fluids, and frequent environmental surface decontamination. The majority of MRSA patients in this facility remained either colonized or became recolonized during a 30-day follow-up period after treatment. Furthermore, a most disturbing byproduct of the Portland VA study was the emergence of resistance to rifampin after therapy.

Case 3: Coordination of infection control practices between a hospital and nursing homes to manage MRSA (Jewell, 1994)

The Christ Hospital and Medical Center, Oak Lawn, Illinois, is an 823-bed teaching hospital that serves many patients who live in regional nursing homes. Before 1991, nursing homes often required three successive test results showing the patient was not carrying MRSA before they would accept a patient from the hospital. This led to extended stays in the hospital for patients who were colonized with MRSA, but otherwise did not need to be in the hospital. A quality improvement team including clinicians, hospital administrators, and nursing home representatives adopted guidelines that allowed colonized patients to be returned to the nursing homes. When these new guidelines were adopted, the hospital did not see any change in the number of patients infected or colonized with MRSA. It did see an average decrease of over 10 days in the length of stay in the hospital, a reduction in the readmission rate of patients colonized with MRSA from 8.7 to 2.7 percent in 1992, and total cost savings of over $1.9 million.

These case studies illustrate the complexities in determining which infection control practices are the most likely to help control antibiotic-resistant bacteria such as MRSA. In the first case, a combination of isolation of patients colonized or infected with MRSA and antibiotic therapy seemed to control MRSA, but in the second case similar procedures failed to produce posi-

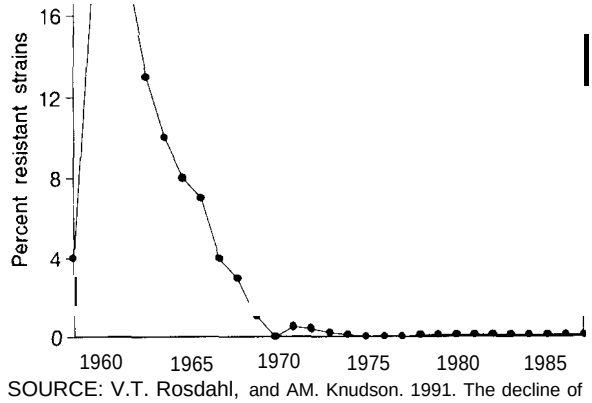
tive results. Further, the second case illustrates a danger in antibiotic-therapy for decolonization: the emergence of new antibiotic-resistant strains. And the third case illustrates that isolation of patients colonized with antibiotic-resistant bacteria can be taken too far: in this case allowing patients colonized with MRSA to return to nursing homes saved money and significantly reduced the length of hospital stays. Hospitals and nursing homes need to examine cases such as these along with specific conditions in their own facilities to determine the best practices for reducing the spread of antibiotic-resistant bacteria.

BOX 4-2: Methicillin-Resistant *Staph. aureus* and Infection Control in Denmark

In Denmark the frequency of methicillin-resistant *Staph aureus* (MRSA) rose to 15 percent between 1967 and 1971, but decreased to 0.2 percent by 1984, and has remained at that low level (see figure).

Hans Jern Kolmos of the Hvidovre Hospital, University of Copenhagen, discussed the dramatic decline in MRSA at a recent meeting of the Association of Practitioners of Infection Control and Epidemiology. Kolmos attributes the decline to strict control of antibiotic use in hospitals. He acknowledges one of the fundamental dilemmas in antibiotic prescribing: "In a situation of doubt, where the clinician stands face to face with an ill patient, fear of overlooking an infection-or pressure from the patient—will often outweigh the fear of side effects in the doctor's mind, and the result will be prescription for safety's sake, " Kolmos stresses the value of including clinical microbiologists in the decision-making process: "In Denmark the clinical microbiologist is a medical doctor, who has a clinical education in addition to his laboratory education. This means that he takes part not only in laboratory work, but also in the treatment of patients, either bedside or at conferences with the clinical staff. Formally, he is only an advisor; it is the clinician who has the power to decide. However, the influence of the clinical microbiologist is great, partly because he is well-known from his frequent visits to the clinical units and partly because he has the same educational background as the clinicians. "

Frequency of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in **Denmark**



SOURCE: V.T. Rosdahl, and AM. Knudson. 1991. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology 12(2):83-88.*

The low rates of MRSA in Denmark may also be due to strict compliance with infection control procedures. Westh et al. (1992) note that "Isolation of a methicillin-resistant strain triggers an immediate visit to the patient involved and the staff caring for that patient by a microbiologist and an infection control nurse. Patients are isolated, and hygienic precautions are taken in an effort to prevent acquisition and carriage of the resistant strain by staff members. " They also comment that "Such precautions at institutions in countries not yet overwhelmed by high rates of isolation of methicillin-resistant S. *aureus* might likewise hinder the spread of these strains. "

SOURCES: V.T. Rosdahl and A.M. Knudson, 1991. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology* 12(2):83-88; H. Westh, J.0. Jarlov, H. Kjersem, et al. 1992. The disappearance of multiresistant *Staphylococcus aureus in* Denmark: Changes in strains of the 83A complex between 1969 and 1989. *Clinical Infectious Diseases* 14(6) .1186-1194

HOSPITAL ACCREDITATION AND INFECTION CONTROL REGULATIONS UNDER MEDICARE

Current hospital accreditation and Medicare regulations recognize that each hospital must analyze conditions in its own facility to determine the best methods of infection control.

Loeb and O'Leary of The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) explain that

> The Joint Commission historically has used compliance with contemporary standards as its basic measure of health care quality in the accreditation process. In recent years, however, there has been growing interest in monitoring and evaluating the actual results of care. . .

JCAHO has recently developed a system for performance measurement called the Indicator Measurement System (IMSystem). Beginning in 1996, the system will include several measurements related to antibiotic use and infection control: timing of administration of prophylactic antibiotics, surveillance and prevention of surgical site infection, surveillance and prevention of ventilator-associated pneumonia, and surveillance and prevention of primary blood stream infections. JCAHO has recognized ". . . the already tremendous information burdens on most organizations" and therefore has designed

> ". . . the IMSystem to be parsimonious, that is, to collect only those data elements that are needed and to use all the elements that are collected. Whenever possible, the IMSystem uses data elements likely to be already collected by health care organizations" (IMSystem General Information, JCAHO).

Participation in this system, which is voluntary, has great potential to help hospitals identify specific problems in infection control.

Medicare regulations state that as a condition of participation in Medicare, hospitals must have a quality assurance program in which "nosocomial infections and medication therapy must be evaluated" (42 CFR 482.21a2). Further, "there must be an active program for the prevention, control, and investigation of infectious and communicable diseases" (42 CFR 482.42). This program includes the designation of an infection control officer who "must develop a system for identifying, reporting, investigating, and controlling infections and communicable diseases of patients and personnel" (42 CFR 482.42a1) and "must maintain a log of incidents related to infections and communicable diseases" (42 CFR 482.42a2).

In the past, regulations for accreditation and Medicare participation were more specifically worded, and specifically acknowledged the problems of antibiotic resistance: for example, hospitals had to have "measures which control the indiscriminate use of preventive antibiotics in the absence of infection, and the use of antibiotics in the presence of infection is based on necessary cultures and sensitivity tests" (42 CFR 405.1022c6 as of Oct. 1, 1983). However, based on past experiences such as those described in this chapter, specific regulations such as these may not be applicable to every facility.

Surveillance of Antibiotic-Resistant Bacteria

There is no national system for reporting the presence and pattern of antibiotic-resistant bacteria, leaving physicians and scientists in the dark about the prevalence of those organisms in different geographical areas. Although many in-hospital, small-scale surveillance systems, designed to track the spread of disease-causing organisms, including antibiotic-resistant bacteria, provide information to physicians about which antibiotics remain effective, there is no standard format for the collection and dissemination of data. Antibiotic prescriptions and microbiology test results are often recorded on separate slips of paper, making correlation of the two sets of data almost impossible. However, the increasing use of computer technology and the Internet provides increased opportunities for standardized record keeping in hospitals and easy database collection and access.

At the state level, the New Jersey State Department of Health started collecting data about antibiotic-resistant bacteria in 1991. The

system includes the 95 acute-care hospitals licensed by the State of New Jersey and uses data that are already routinely collected in hospital laboratories. All hospitals make monthly reports to the State Department of Health, which, in turn, disseminates its compilation of information to anyone on request. This system's tracking of vancomycin-resistant Enterococcus (VRE) spurred collaborative efforts involving private and public sector and academic organizations to evaluate risk factors for the disease, treatment options, effectiveness of infection-control procedures, and the in-vitro susceptibility of VRE to antimicrobial agents during the planning of clinical trials (MMWR, 1995). The system is inexpensive to operate and simple to maintain.

SCOPE, Surveillance and Control of Pathogens of Epidemiological Importance, is a national effort established by the University of Iowa and Lederle Laboratories (now Wyeth-Ayerst Lederle Laboratories) in 1995. The program expects to collect reports of all nosocomial bloodstream infections in 48 hospitals nationwide as well as samples of the organisms isolated from the infected patients. The reports will provide information about the spread of antibiotic-resistant bacteria in the participating hospitals. The bacterial samples will be banked at the University of Iowa, and the accuracy of bacterial identification and antibiotic resistance determinations will be verified for representative samples. For a fee, the University will test new antibiotics from any company against bacteria in its collection. The first hospital entered the program on April 1, 1995, and 40 had entered by June 30.

There are also other industry-funded surveillance systems. A number of academic and commercial laboratories conduct surveillance under contract to pharmaceutical companies, but they are not necessarily designed to obtain information most useful for public health purposes. Instead, and understandably, they collect information about the efficacy of producers' products.

The National Nosocomial Infection Survey (NNIS), which is run by CDC, is the single nationwide surveillance system that produces information about antibiotic-resistant bacteria. While it is limited to reports on nosocomial infections, it is the source for most of the data in this OTA report about MRSA, VRE, and other drug-resistant bacterial infections.

CDC is in the early stages of establishing nationwide surveillance of drug-resistant *Streptococcus pneumoniae* (DRSP), which will cover infections whether or not they occur in a hospital. The system requires that participating laboratories test all *S. pneumoniae* isolated from blood and cerebrospinal fluid for antibiotic susceptibility by using standard testing methods, and that all test results be reported to the state health departments. The CDC initiated this system in 20 laboratories in New Jersey in April 1995, and if funds are available, the organization expects that most of the nearly 2,000 hospital and commercial laboratories that now have computerized record keeping will be in the system by 1998. As laboratories add computer capabilities, CDC will encourage them to enlist in the system, and it expects that all of the nearly 5,000 laboratories in the country will participate. If the DRSP system works, CDC envisions expanding it to include other antibiotic-resistant bacteria. As an early step in setting up the DRSP system, and at CDC's request, the Council of State and Territorial Epidemiologists has recommended DRSP for inclusion on the list of notifiable diseases, and four states now report it.

WHONET, a surveillance project of the World Health Organization, was established and operated by two scientists, and it functions on a shoestring budget. The system collects information about resistance patterns in bacteria from about 100 hospitals all over the world, makes the data available to researchers, and provides much of the available information about the international flow of antibiotic-resistant bacteria.

One of WHONET's great strengths is that it has demonstrated that laboratories around the world can produce data that can be interpreted and incorporated into a system that provides results that are comparable from country to country. To do this, the network collects laboratory data, not interpretations of the data. While rules for interpreting susceptibility test results differ

among various countries, WHONET can make international comparisons based on the raw data.

Participating institutions also gain from WHONET. The network provides laboratories with a computer program, which can be taught in about six hours, and, where necessary, a computer. The software of WHONET, set up to identify unusual patterns of resistance, allows the infection control practitioner at the hospital to trace the spread of individual strains of bacteria and use that information to modify infection control procedures.

WHONET is inexpensive, it requires little supervision, and it obtains raw data, the data of most value to researchers (see chapter 6). It has been successful in obtaining information from developing countries as well as developed ones, and it provides an example of the feasibility of collecting and reporting antibiotic-resistance information for little money.

Controlling the Use of Antibiotics

Much evidence links the use of antibiotics to the emergence and spread of antibiotic resistance. Table 4-3 summarizes some studies which demonstrate relationships between *increased* use of antibiotics and prevalence of resistance in hospital organisms. There are also many examples where the prevalence of resistance in hospital organisms *decreased* when the use of antibiotics was *decreased* (table 4-4). McGowan (1994) recently asked the question: "Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance?" and concluded that

TABLE 4-3: Some Studies Demonstrating a Temporal Relationship Between *Increased* Usage of Antimicrobial Agents and *Increased* Prevalence of Resistant Hospital Organisms

Year	Reference	Setting for use of antimicrobials	Organism(s)	Antimicrobial(s) used
1953	1	General use	*Staphylococcus aureus*	Erythromycin
			S. aureus	Penicillin
			S. aureus	Chlortetracycline
1956	2	Burn ward	*S. aureus*	Chloramphenicol
			S. aureus	Chlortetracycline
1967	3	Surgical prophylaxis	*S. aureus*	Neomycin cream
1971	4	Burn ward	*Pseudomonas aeruginosa*	Gentamicin
1978	5	Surgical prophylaxis	*P. aeruginosa*	Gentamicin
			Serratia	Gentamicin
1979	6	Postoperative use	*Serratia*	Gentamicin

1. M.H. Lepper, B. Moulton, H.F. Dowling, et al. 1953. Epidemiology of erythromycin-resistant staphylococci in a hospital population—effect on the therapeutic activity of erythromycin. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1953–1954*. New York, NY. Medical Encyclopedia, pp. 308–313.

2. C.D. Gibson, Jr., and W.C. Thompson, Jr. 1956. The response of burning wound staphylococci to alternating programs of antibiotic therapy. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1955–1956*. New York, NY. Medical Encyclopedia, pp. 32–34.

3. P.M. Rountree, M.A. Beard, J. Loewenthal, et al. 1967. Staphylococcal sepsis in a new surgical ward. *British Medical Journal* 1:132–137.

4. J.A. Shulman, P.M. Terry, and C.E. Hough. 1971. Colonization with gentamicin-resistant *Pseudomonas aeruginosa*, pyocine type 5, in a burn unit. *Journal of Infectious Disease* 124(suppl):S18–23.

5. N.J. Roberts, Jr., and R.G. Douglas, Jr. 1978. Gentamicin use and *Pseudomonas* and *Serratia* resistance: effect of a surgical prophylaxis regimen. *Antimicrobial Agents and Chemotherapy* 13:214–220.

6. V.L. Yu, C.A. Oakes, K.J. Axnick, et al. 1979. Patient factors contributing to the emergence of gentamicin-resistant *Serratia marcescens*. *American Journal of Medicine* 66:468–472.

SOURCE: J.E. McGowan, Jr. 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Reviews of Infectious Diseases* 5(6):1033–1048.

TABLE 4-4: Some Studies Demonstrating a Temporal Relationship Between *Decreased* Usage of Antimicrobial Agents and *Decreased* Prevalence of Resistant Organisms

Year	Reference	Setting for use of antimicrobials	Organism(s)	Antimicrobial(s) used
1953	1	General use	*Staphylococcus aureus*	Chloramphenicol
1954	2	General use	*S. aureus*	Erythromycin
1956	3	Burn ward	*S. aureus*	Chlortetracycline
			S. aureus	Chloramphenicol
1960	4	General use	*S. aureus*	Penicillin
1960			*S. aureus*	Tetracycline
1966	5	Pediatric ward	*S. aureus*	Erythromycin
1967	6	Surgical prophylaxis	*S. aureus*	Neomycin cream
1970	7	General use	*Escherichia coli*	Streptomycin
			Klebsiella, Enterobacter	Streptomycin
1970	8	Neurosurgical unit	*Klebsiella*	"All"
1970	9	General use	*S. aureus*	Erythromycin
			S. aureus	Novobiocin
1971	10	Burn ward	*Pseudomonas aeruginosa*	Gentamicin
1972	11	Burn ward	*"Enterobacteriaceae"*	Carbenicillin
			Pseudomonas aeruginosa	Carbenicillin
1973	12	Nursery	*"Enterobacteria"*	Carbenicillin
1974	13	Urology ward	*"Gram-negative bacilli"*	5 agents
1975	14	Nursery	*E. coli*	Kanamycin
1978	15	Surgical prophylaxis	*Pseudomonas aeruginosa*	Gentamicin
	16		*Serratia*	Gentamicin

1. W.M.M. Kirby, and J.J. Ahern. 1953. Changing pattern of resistance of staphylococci to antibiotics. *Antibiotics and Chemotherapy* 3:831–835.
2. M.H. Lepper, B. Moulton, H.F. Dowling, et al. 1953. Epidemiology of erythromycin-resistant staphylococci in a hospital population—effect on the therapeutic activity of erythromycin. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1953–1954*. New York, NY. Medical Encyclopedia, pp. 308–313.
3. C.D. Gibson, Jr., and W.C. Thompson, Jr. 1956. The response of burning wound staphylococci to alternating programs of antibiotic therapy. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1955–1956* New York, NY. Medical Encyclopedia, pp. 32–34.
4. M. Barber, A.A.C. Dutton, M.A. Beard, et al. 1960. Reversal of antibiotic resistance in hospital staphylococcal infection. *British Medical Journal* 1:11–17.
5. A.W. Bauer, D.M. Perry, and W.M.M. Kirby. 1960. Drug usage and antibiotic susceptibility of staphylococci. *Journal of the American Medical Association* 173:475–480.
6. J.O. Forfar, A.J. Keay, A.F. Maccabe, et al. 1966. Liberal use of antibiotics and its effect in neonatal staphylococcal infection, with particular reference to erythromycin. *Lancet* 2:295–300.
7. P.M. Rountree, M.A. Beard, J. Loewenthal, et al. 1967. Staphylococcal sepsis in a new surgical ward. *British Medical Journal* 1:132–137.
8. R.J. Bulger, E. Larson, and J.C. Sherris. 1970. Decreased incidence of resistance to antimicrobial agents among *Escherichia coli* and *Klebsiella-Enterobacter*: observations in a university hospital over a 10-year period. *Annals of Internal Medicine* 72:65–71.
9. D.J.E. Price, and J.D. Sleigh. 1970. Control of infection due to *Klebsiella aerogenes* in a neurosurgical unit by withdrawal of all antibiotics. *Lancet* 2:1213–1215.
10. M. Ridley, D. Barrie, R. Lynn, et al. 1970. Antibiotic-resistant *Staphylococcus aureus* and hospital antibiotic policies. *Lancet* 1:230–233.
11. J.A. Shulman, P.M. Terry, and C.E. Hough. 1971. Colonization with gentamicin-resistant *Pseudomonas aeruginosa*, pyocine type 5, in a burn unit. *Journal of Infectious Disease* 124(suppl):S18–23.
12. E.J.L. Lowbury, J.R. Babb, and E. Roe. 1972. Clearance from a hospital of gram-negative bacilli that transfer carbenicillin-resistance to *Pseudomonas aeruginosa*. *Lancet* 2:941–945.
13. J.A. Franco, D.V. Eitzman, and H. Baer. 1973. Antibiotic usage and microbial resistance in an intensive care nursery. *American Journal of Diseases of Children* 126:318–321.
14. H. Søgaard, C. Zimmermann-Nielsen, and K. Siboni. 1974. Antibiotic-resistant gram-negative bacilli in a urological ward for male patients during a nine-year period: relationship to antibiotic consumption. *Journal of Infectious Disease* 130:646–650.
15. J.B. Howard, and G.H. McCracken, Jr. 1975. Reappraisal of kanamycin usage in neonates. *Journal of Pediatrics* 86:949–956.
16. D.L. Palmer. Epidemiology of antibiotic resistance. 1980. *Journal of Medicine* 11:255–262.

SOURCE: J.E. McGowan, Jr. 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Reviews of Infectious Diseases* 5(6):1033–1048.

> . . . in a few institutions there has been an increase in susceptibility to antimicrobials following intensive control or monitoring . . . in a few hospitals, intensive antibiotic control for selected drug-organisms pairs was associated with a high prevalence of susceptibility, and the proportion susceptible fell abruptly when control or monitoring was relaxed or removed.

This latter finding indicates that the decrease in resistance may not be stable: reintroduction of the antibiotic can cause the resistance to immediately return.

There are also counterexamples where antibiotic control programs do not increase susceptibility. In one example, resistance patterns in *Enterobacter cloacae* but not *Pseudomonas aeruginosa* were related to ceftazidime use in 18 different hospitals in different geographical locations (Ballow and Schentag, 1992). Silber et al. found that "facilities with restriction programs were as likely as those without to have had a case of VRE bacteremia." In Denmark the use of methicillin *increased* substantially in the 1970s while the prevalence of MRSA *decreased* substantially. The decrease in MRSA was correlated with a decrease in the use of tetracycline and streptomycin (Rosendal et al., 1977). This might be explained by the use of tetracycline and streptomycin selecting for bacteria with multi-resistant plasmids (see chapter 2) also containing genes for resistance to methicillin. Taken together, these examples indicate that it is not simple to determine the specific relationship between antibiotic use and antibiotic resistance.

CDC recently began a systematic study of the relationship between antibiotic use and antibiotic resistance. In the initial phase of the I-CARE (Intensive Care Antimicrobial Resistance Epidemiology) project, eight pilot hospitals monitored the use of antibiotics and the numbers of antibiotic-resistant bacteria. The results for MRSA (shown in figure 4-4) indicate that some hospitals use large amounts of methicillin and have high frequencies of resistant organisms (hospital B), while others use very little methicillin, but still have high frequencies of resistant organisms (hospital E).

One possible explanation for this is suggested by the Klebsiella results in figure 4-5: hospital E may be receiving many patients from another hospital (or nursing home) that uses a lot of methicillin. Hospital H is interesting in that it has one of the lowest rates of MRSA and the highest use of methicillin of any of the eight pilot hospitals. This result might be related to a recent result from a French 15-year study (Loulergue et al., 1994) that showed the prevalence of MRSA was unrelated to cloxacillin (a semisynthetic penicillin derivative closely related to methicillin) use on some wards of a hospital where none of the staff was a carrier of MRSA. This study indicated that carriage of MRSA by hospital staff is one risk factor for patients becoming infected with MRSA. The data from I-CARE correlate the emergence and spread of antibiotic resistance with different causes in different hospitals. Moreover, the pilot study demonstrates how useful a system such as I-CARE can be in comparing an individual hospital to national trends and using that comparison to design antibiotic use and infection control procedures specifically tailored to the problems in the individual hospital.Antibiotics are widely used by physicians in community practice as well as by physicians in the hospitals. In one study (table 4-5), about half of the cardiac surgery patients colonized with cefazolin-resistant strains of bacteria were colonized upon admission to the hospital.[5] Therefore, some antibiotic-resistant strains arise in the community, indicating that antibiotic use must be

[5] Cefazolin is commonly administered to cardiac patients as prophylaxis to prevent infections during the surgery. The risk of developing a *Staph. aureus* infection after cardiac surgery has been estimated as 15-44 percent (Mandell, Bennet, Dolin, page 2747). Colonization of the patient or attending staff with cefazolin-resistant strains would be a significant risk factor for surgical infections when cefazolin is used for prophylaxis.

FIGURE 4-4a: Percent of *Staphylococcus Aureus* Resistant to Methicillin

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-4b: Grams of Methicillin Used per 1,000 Patient Days

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-4c: Percent of *Staphylococcus aureus* Resistant to Methicillin/Methicillin Use

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

controlled by community physicians as well as by hospital physicians in order for hospital-based programs to be fully effective. (For more information about antibiotic-resistant bacteria and antibiotic use in the community, see chapter 3.

Improving Antibiotic Use

Antibiograms

To guide physicians in the use of antibiotics, many hospitals provide "antibiograms" that describe the susceptibility of commonly encountered bacteria to various antibiotics. As shown in table 4-6, the vast majority of causes of bacterial infections in both inpatients and outpatients remain sensitive to the modern antibiotics. On the other hand, many *Staph. aureus*, coagulase-negative Staphylococci, and *S. pneumoniae* are resistant to many commonly used antibiotics, and some Enterococcus are resistant to all antibiotics.

Formularies

The use of all drugs in hospitals is increasingly controlled by hospital formularies, which were set up to control the costs of drugs. The formularies may have the added benefit of helping to control the use of antibiotics and the antibiotic resistance problem. In Denver, Colorado, area hospitals (North, 1993), a formulary is combined with a computerized antibiotic order form. This system restricts some antibiotics to approved indications, and use of others requires approval by specialists in infectious disease. This system has saved the hospitals money, and allowed them to easily change the formulary when susceptibility testing indicated a problem of increased resistance to a specific antibiotic) .

Physician Education

Physician education is crucial to avoid mistakes made by inadequate knowledge of antibiotic

FIGURE 4-4a: Percent of *Staphylococcus Aureus* Resistant to Methicillin

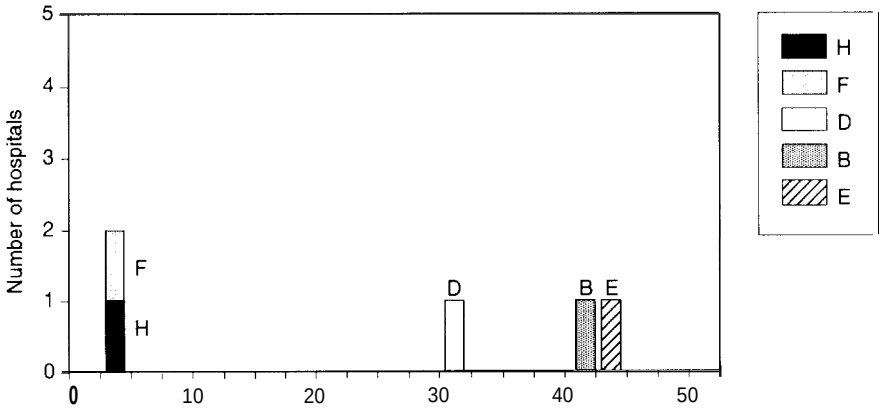


FIGURE 4-4b: Grams of Methicillin Used per 1,000 Patient Days

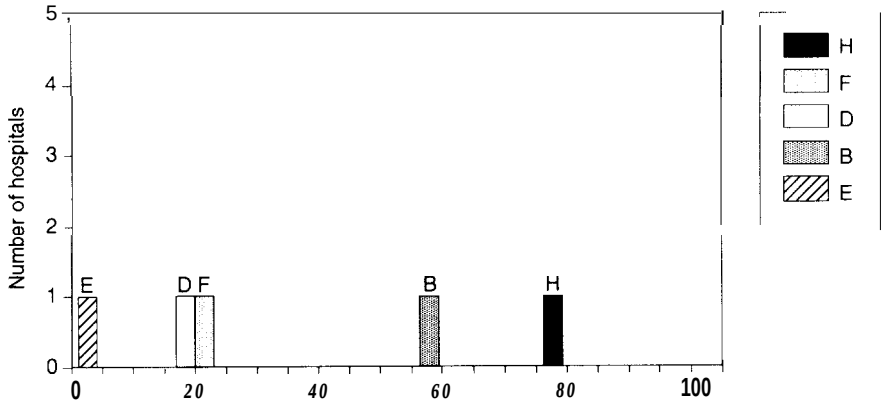
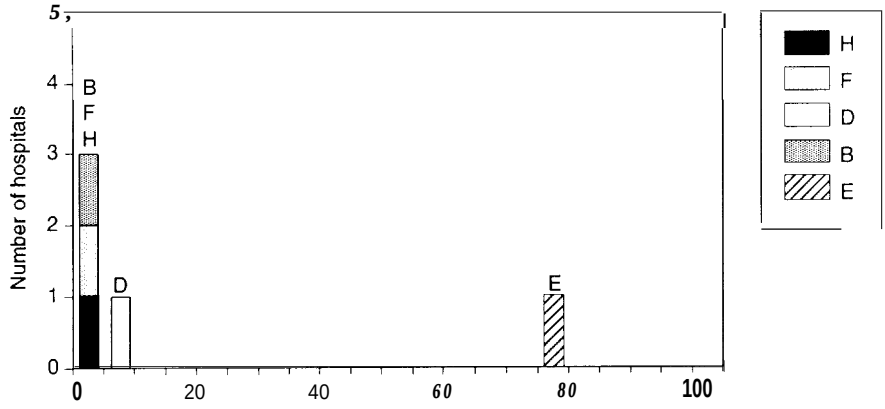
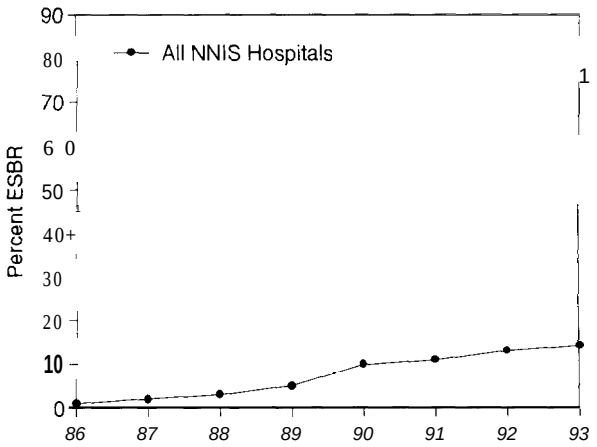


FIGURE 4-4c: Percent of *Staphylococcus aureus* Resistant to Methicillin/Methicillin Use



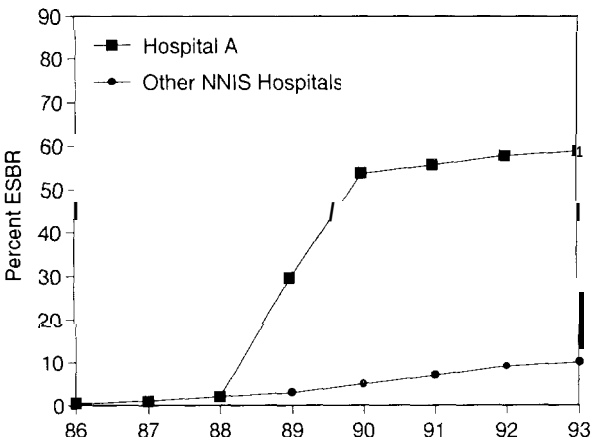
SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-5a. All Hospitals in the National Nosocomial Infection Surveillance System



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

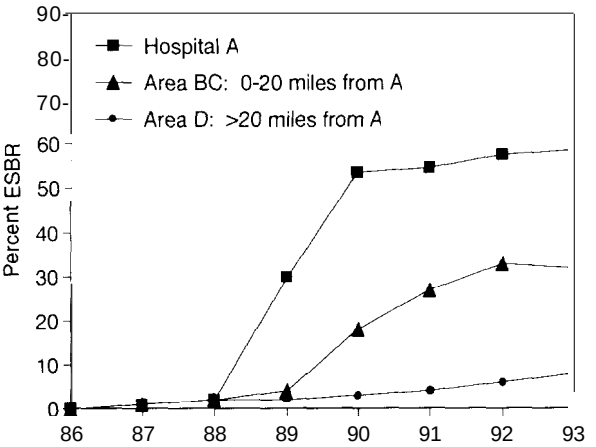
FIGURE 4-5b: Hospital A and All NNIS Hospitals



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

controlled by community physicians as well as by hospital physicians in order for hospital-based programs to be fully effective. (For more information about antibiotic-resistant bacteria and antibiotic use in the community, see chapter 3.

FIGURE 4-5c. Hospital A and Surrounding Areas



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

Improving Antibiotic Use

Antibiograms

To guide physicians in the use of antibiotics, many hospitals provide "antibiograms" that describe the susceptibility of commonly encountered bacteria to various antibiotics. As shown in table 4-6, the vast majority of causes of bacterial infections in both inpatients and outpatients remain sensitive to the modern antibiotics. On the other hand, many *Staph. aureus,* coagulase-negative Staphylococci, and *S. pneurnoniae* are resistant to many commonly used antibiotics, and some Enterococcus are resistant to all antibiotics.

Formularies

The use of all drugs in hospitals is increasingly controlled by hospital formularies, which were set up to control the costs of drugs. The formularies may have the added benefit of helping to control the use of antibiotics and the antibiotic resistance problem. In Denver, Colorado, area hospitals (North, 1993), a formulary is combined with a computerized antibiotic order form. This system restricts some antibiotics to approved indications, and use of others requires approval

TABLE 4-5: Characteristics of Cardiac Surgery Patients Colonized with Cefazolin-Resistant Gram-Negative Bacilli

Species	Number of patients colonized (n = 87)	Location at first positive culture (% patients)			Percent of colonization due to horizontal transmission	Percent developing clinical infection
		At admission	48–72 hr into CSICU	> 72 hr into CSICU		
Enterobacter species	58	50	34	16	16	21
Citrobacter species	37	49	22	29	?	3
Pseudomonas aeruginosa	33	55	12	33	9	27
Serratia marcesens	7	43	57	0	29	29

KEY: CSICU = cardiac surgery intensive care unit; ? = unknown (no typing system used).

SOURCE: Adapted from D.M. Flynn, R.A. Weinstein, and S.A. Kabins. 1988. Infections with gram-negative bacilli in a cardiac surgery intensive care unit: The relative role of *Enterobacter*. *Journal of Hospital Infections* 11:367.

tion about susceptibilities of different organisms. Physicians must learn to check other reliable up-to-date sources of information about antibiotics such as *The Medical Letter On Drugs and Therapeutics* (New Rochelle, NY: The Medical Letter, Inc.) and to consult with infectious disease experts who are aware of susceptibility patterns in the specific hospitals.

Computerized Systems for Antibiotic Monitoring

The LDS Hospital in Salt Lake City, Utah, has developed a computerized antibiotic monitoring system, which is part of a larger computerized patient record system that automatically collects surveillance data and generates antibiograms (see table 4-6) (Evans and Pestotnik, 1994). When the microbiology laboratory results are entered into the computer, the computer checks the susceptibilities of the organisms against the antibiotic prescribed for the patient and generates an alert when an antibiotic is inappropriate. In one year, the system generated an alert for 32 percent of the patients. However, many physicians did not change the antibiotic based on the alert, often because the patient was clinically improving even though the susceptibility results indicated that the antibiotic was inappropriate.[6] The system also notifies physicians of the optimum time for administration of prophylactic antibiotics. Use of the system saved $42 per patient in the first year of use, with a projected reduction in the costs of prophylactic antibiotics of over $89,000 per year in a single hospital (Evans et al., 1990).

Another part of the antibiotic monitoring system at the LDS hospital is a computerized antibiotic consultant (Evans et al., 1994). This system uses surveillance data together with information about the site of the infection and patient allergies to determine the best choice of empiric antibiotic therapy. The computer consultant was better at choosing antibiotics than the physicians in the hospital. The computer chose antibiotics to which the infecting bacteria were susceptible 94 percent of the time; the physicians chose correctly 77 percent of the time.

Setting up a comprehensive patient data system requires significant financial investment by hospitals. However, the hospitals will realize cost savings just from improvement in the use of antibiotics. Forty to fifty percent of hospital

[6] Many patients recover from bacterial illnesses on their own without the help of an antibiotic.

TABLE 4-6: Antibiotic Susceptibility of Common Organisms (Numbers Indicate Percent Susceptible) January–December 1994 (Page 1 of 2)

IN PATIENTS	Staph. aureus (1080)	Coagulase-neg. Staph. (647)	Strep. pneumoniae (75)	Enterococcus spp. (612)	E. coli (808)	K. species (396)	C. diversus (35)	C. freundii (42)	Enterobacter species (309)	Serratia species (55)	Proteus mirabilis (100)	P. aeruginosa (520)	A. anitratus (60)	X. maltophilia (42)	H. influenzae (128)	B. fragilis group (30)
Penicillin	5	6	86													3
Ampicillin				88	54	0	0	0	0	0	91				75	
Ampicillin-sulbactam	***	***			58	59	91	50	15	13	97		54	0		93
Oxacillin	70	26														
Ticar-clavulante*	***	***			77	75	96	62	61	88	100	67	58	52		100
Cephalothin**	***	***			73	71	97	3	1	0	94					
Cefazolin	***	***			88	78	97	7	3	0	97					
Cefotetan	***	***			99	88	97	68	55	92	99					70
Cefuroxime	***	***													99	
Cefotaxime	***	***	93		99	95	97	77	66	94	99				100	76
Ceftazidime												84	69	23		
Imipenem	***	***						100	100				96	0		
Chloramphenicol															99	
Erythromycin			91													
Trimeth-sulfa	83	39	77		80	77	100	58	88	93	95		70	90	88	
Ciprofloxacin	70	54		21	99	98	100	100	96	99	100	82	61	14		
Nitrofurantoin				87	96	61			45		15					
Gentamicin					97	91	95		93	100	98	84	66	50		
Amikacin****					100	98			99			84	91	35		
Clindamycin	72	48														92
Metronidazole																100
Vancomycin	100	100		99												

* Piperacillin-tazobactam was added to the formulary late in the year. Its activity is equivalent to or somewhat superior to ticarcillin-clavulanate.

** Tested for the oral cephalosporins, cephalexin and cephradine.

*** Oxacillin-resistant staphylococci are also resistant to beta-lactamase inhibitor combinations, cephalosporins, and imipenem; oxacillin-susceptible staphylococci are susceptible to those agents.

**** Amikacin reported only on Gentamicin resistant isolates.

TABLE 4-6: Antibiotic Susceptibility of Common Organisms (Numbers Indicate Percent Susceptible) January–December 1994 (Page 2 of 2)

OUT PATIENTS	Staph. aureus (966)	Coagulase-neg. Staph. (320)	Strep. pneumoniae (103)	Enterococcus spp. (632)	Escherichia coli (2558)	K. species (405)	C. diversus (76)	C. freundii (48)	E. species (136)	Serratia species (46)	Proteus mirabilis (244)	P. aeruginosa (234)	Salmonella species (25)	Shigella species (51)	H. influenzae (121)
Penicillin	4	13	83												
Ampicillin				94	53	2	0	6	2	0	89		92	33	72
Ampicillin-sulbactam	***	***			72	75	95	81	37	12	97				
Oxacillin	89	52													
Ticar-clavulante*	***	***			90	90	100	90	92	93	100	85			
Cephalothin**	***	***			65	86	96	3	3	0	94				
Cefazolin	***	***			90	91	97	13	4	0	93				
Cefotetan	***	***			99	97	100	91	83	90	100				
Cefuroxime	***	***													100
Cefotaxime	***	***	92		99	98	100	94	92	94	100		100		100
Ceftazidime												95			
Chloramphenicol													92	87	100
Erythromycin			84												
Trimeth-sulfa	92	54	80		81	83	100	61	94	88	93		100	70	94
Ciprofloxacin	88	72		24	99	97	97	92	97	96	99	87	100	100	
Nitrofurantoin				91	99	62	91	90	51	0	0				
Gentamicin					99	96	100	97	98	95	95	93			
Amikacin****					93						100	93			
Clindamycin	91	76													
Vancomycin	100	100		100											

* Piperacillin-tazobactam was added to the formulary late in the year. Its activity is equivalent to or somewhat superior to ticarcillin-clavulanate.
** Tested for the oral cephalosporins, cephalexin and cephradine.
*** Oxacillin-resistant staphylococci are also resistant to beta-lactamase inhibitor combinations, cephalosporins, and imipenem; oxacillin-susceptible staphylococci are susceptible to those agents.
**** Amikacin reported only on Gentamicin resistant isolates.

KEY: Staph. = Staphylococci
Strep. = Strephcoccus
K. species = Klebsiella species
C. diversus = Citrobacter diversus
C. freundii = Citrobacter freundii
E. species = Enterobacter species
P. aeruginosa = Pseudomonas aeruginosa
A. anitratus = Acinetobacter anitratus
X. = Xanthomonas maltophilia
H. influenzae = Haemophilus influenzae
B. tragillis group = Bacteroides tragillis group

SOURCE: University Health System, San Antonio, TX, 1994. With permission of J.H. Jorgensen.

BOX 4-3: "Food-Borne" Outbreak of Expensive Antibiotic Use in Community Teaching Hospital

To the Editor—Drug utilization review assures cost-effective use of medications in hospitals. We present an example of drug utilization review that began with the identification of an "index case" of a costly therapeutic decision. Subsequent investigation lead to the identification of a prescribing outbreak as well as its probable source.

Report of a Case—A 32-year-old man had been on a camping trip and noted an insect bite at the top margin of his sock. The next day he noted redness and swelling at the site of the bite. The third day he was febrile and the redness began to spread. On the fourth day, red streaks extended 15 cm above the site of injury. He felt ill and came to the emergency department. His examination demonstrated a temperature of 39.4°C, sickly appearance, and a tender cellulitis of his lower leg. Blood pressure was normal and he did not have a truncal rash. Therapy with a new, expensive, broad-spectrum antibiotic was initiated. When asked about his antibiotic choice, the admitting intern noted at morning report that he had planned on giving penicillin or nafcillin, but had been overruled by the supervising resident who insisted on a "more modern choice for a severely ill patient."

Comment—Following discussion of this case, we evaluated the use of the new antibiotic in our hospital. We found that use had transiently increased following its addition to our formulary in February 1994, then abruptly increased in June and July. After conducting interviews with our house officers, it was revealed that an extravagant dinner party had been held for incoming and current house staff the third week of June. The sponsor of this dinner was the manufacturer of the antibiotic. The increase in use of this agent bore a striking temporal association with this dinner. Furthermore, the prescribing resident had attended the dinner and directed the admitting intern to use the drug instead of nafcillin.

The prescribed antibiotic exhibits a broad spectrum of activity, including β-lactamase-producing strains of staphylococci, *Haemophilus influenzae*, anaerobes, and facultative gram-negative rods. The agent would be expected to be effective in most settings where nafcillin might be used. Although this agent is not contraindicated in treating uncomplicated cellulitis, it is much more expensive ($183.20 per day) than other effective drugs such as nafcillin ($84 per day). In this single case, the daily excess cost of therapy would approximate $100. The relationship between pharmaceutical marketing maneuvers and prescribing is controversial. Previous ecological studies have found an association between educational "enticements" and hospital formulary additions and prescribing trends. However, we are not aware of a detailed case description where a more expensive therapeutic choice was made when less expensive therapeutic alternatives were indicated. We do not know if the resident's attendance at the dinner caused his therapeutic choice. However, the striking epidemiological association between resident attendance at this drug company-sponsored event and the subsequent changes in hospital-wide prescribing practices should prompt training programs to be wary of such outside sources of medical education.

SOURCE: Quoted from R.I. Shore and W.L. Greene, letter to the editor, *Journal of the American Medical Association* 273(24):1908. Copyright 1995, American Medical Association.

FIGURE 4-6: An Antibiotic Advertisement from a Medical Journal



SOURCE: A major pharmaceutical company.

pharmacy budgets are for antibiotics, and one-fourth of that in some hospitals is for vancomycin alone (*Modern Healthcare*, 1994). Eliminating unnecessary use of antibiotics will decrease total pharmacy expenditures. Treating infections with appropriate antibiotics and administering prophylactic antibiotics with appropriate timing will also increase the quality of patient care and decrease the number of days spent in the hospital. (OTA's report *Bringing Health Care Online: The Role of Information Technologies*, September 1995, discusses costs and benefits of computerized patient record systems.)

Practice Guidelines

Practice guidelines, or practice protocols, are medical guidelines that "encompass a broad range of strategies designed to assist practitioners in the clinical decision-making process" (Shanz, 1993). More specifically, they are "standardized specifications for care developed by a formal process that incorporates the best scientific evidence of effectiveness with expert opinion" (Leape, 1990). These guidelines are set by experts from specific areas of the medical profession to advise about recommended standards of care. For example, the goal of practice guidelines established by the Agency for Health Care Policy and Research, a federal agency empowered to establish practice guidelines, is to encourage physicians and other health care providers to change their practice behavior, thus improving patient care, patient outcomes, and quality of life (AHCPR, 1994).

Practice guidelines on infection control or the prudent use of antibiotics might be helpful in controlling antibiotic resistance. For example, practice guidelines might specify that older antibiotics such as amoxicillin be tried for community-acquired infections before newer, broader spectrum antibiotics are used. Under managed care, insurers may adopt guidelines such as these because they will save money as older antibiotics are generally much less expensive than newer antibiotics.

Practice guidelines may also be of use in medical malpractice litigation. A major difficulty in medical malpractice cases is establishing the appropriate standard of care before "layperson" decision-makers on juries. Practice guidelines have the potential to reduce such difficulties. By establishing an unbiased standard of care, practice guidelines should "significantly reduce the most vexing problem in malpractice litigation: the battle of the experts" (West, 1994). In theory, a physician could rely on the practice guideline as the appropriate standard of care without having to worry whether a judge or jury, in a medical malpractice case, would consider the care administered appropriate. The only remaining issues to be determined in medical negligence litigation would be whether the practice guideline "is relevant to the case at hand, and whether it is appropriate to use the [guideline] to establish the standard of care" (West, 1994).

On the other hand, practice guidelines which suggest any benefit from the use of antibiotics may be used as evidence against the physician in the case of a bad outcome. For example, a guideline on the treatment of otitis media with effusion published by the Agency for Health Care Policy and Research concludes:

> Meta-analysis for Guideline development showed a 14 percent increase in the probability that otitis media with effusion would resolve when antibiotic therapy was given versus no treatment. . . . When this small improvement in resolution of otitis media with effusion is weighed against the side effects and cost of antibiotic therapy, antibiotic therapy may not be preferable to observation in management of otitis media with effusion in the otherwise healthy young child. . . . To assist in making choices for management of otitis media with effusion, health care providers need to inform parents fully as to the side effects and costs of antibiotic therapy, as well as the benefits and harms of other options for care (AHCPR, 1994).

A physician who elects not to prescribe an antibiotic, foregoing the 14-percent increased probability that the condition "would resolve," might be held legally liable for any negative outcome. Such potential liability might encourage physicians to prescribe antibiotics even when

they may not be necessary. Further, the above guidelines do not instruct physicians to consider the spread of antibiotic resistance in the decision to prescribe antibiotics. If practice guidelines are going to have an effect on promoting prudent antibiotic use, they have to acknowledge that the benefit to a few patients from routine use of newer and broader spectrum antibiotics may be outweighed by the public health benefits expected from reducing the prevalence of antibiotic-resistant bacteria.

One concern of practice guidelines relevant to antibiotic use is that national standards of conduct do not adequately reflect the localized aspect of antibiotic-resistant bacteria outbreaks. The National Health Lawyers Association addressed this concern in its 1995 Colloquium Report on Legal Issues Related to Clinical Practice Guidelines, which conceded that "[s]ome local adaptation of national guidelines is probably inevitable and may be useful, because even well-developed guidelines may have gaps and may not foresee significant local objectives or constraints" (National Health Lawyers Association Colloquy, 1995). One solution may be the use of an online computer system that allows health care practitioners in a particular geographic area to consult with each other and local experts concerning appropriate local adaptations to practice guidelines (Meyers, 1995). Such a system would also allow health care practitioners to disseminate the specifics of their cases, as well as establish a record of compliance with the practice guidelines in the event of future litigation (Meyers, 1995).

COSTS OF CONTROLLING THE EMERGENCE AND SPREAD OF ANTIBIOTIC-RESISTANT BACTERIA

Hospitals cannot charge costs of infection control procedures and the monitoring of antibiotic-resistant bacteria directly to insurance companies. As a result, although these procedures improve the quality of patient care, hospitals' efforts to minimize costs may retard spending on them. Haley et al. (1987) commented that hospitals might not be placing enough emphasis on infection control because "the direction and magnitude of the financial incentive to prevent nosocomial infections are not clear to many hospital administrators." They analyzed the financial incentives for hospitals to prevent nosocomial infections under the prospective payment system and concluded that

> Assuming an average nosocomial infection rate of 5.7 percent, one would expect. . . a hospital with 10,000 admissions annually to have approximately 570 nosocomial infections per year in the absence of an effective infection control program. If the average 1985 marginal cost of providing extra care for a nosocomial infection were approximately $1800, the total cost of treating these infections would amount to approximately $1 million per year, not counting physicians' fees or medicolegal losses. . . . From the nationwide SENIC project evaluation, we know that at least 32 percent of the infections can be prevented, thus indicating that an effective infection control program could produce a gross financial savings of approximately $305,000 per year. . . nearly five times the costs of the program.

A computerized antibiotic monitoring system, such as that of the LDS Hospital, reduces costs both by controlling the use of antibiotics and reducing the length of hospital stays, but the LDS system has been in development for 20 years, it is based on obsolete computer technology, and it is not exportable. Developing a system on current computer technology will take a significant investment in research and development. Given all the costs involved in control and monitoring, it would be useful to calculate the total cost to hospitals of antibiotic resistance to judge whether infection control procedures and monitoring of antibiotic-resistant bacteria will have a financial payoff.

Many different factors can be considered in a calculation of the cost of antibiotic-resistant bacteria: the direct cost of time in the hospital, the costs of extra physician visits when antibiotics are ineffective, the extra hospitalizations due to community-acquired resistant infections, and the costs of newer antibiotics to replace antibiotics

such as penicillin to which organisms have become resistant. To those must be added the indirect costs to patients from lost days of work, increased illness, and, at worst, death. It is difficult to estimate the costs of all of these factors.

Phelps (1989) made such an estimate and concluded that antibiotic-resistant bacteria cost the nation between $0.1 billion and $30 billion annually. Use of different values for the value of a life accounted for almost all of the 300-fold range in the estimate. The National Foundation for Infectious Disease (1990) estimated that the costs of nosocomial infections caused by antibiotic-resistant bacteria could be as high as $4 billion annually, and CDC has estimated the costs of all nosocomial infections at $4.5 billion per year, an estimate that includes costs from both antibiotic-resistant and susceptible infections.

Here, OTA estimates the effects of antibiotic-resistant bacteria on the costs of some hospitalizations. The national costs of five classes of nosocomial infections—surgical wound infections, pneumonia, bacteremias, urinary tract infections, and others—are taken from the results of the SENIC project (see table 4-1). Those costs are shown on the first data line in table 4-7 (for instance, the cost of all surgical wound infections is $1.6 billion annually). The calculation of the costs of each of the infections caused by each of six different antibiotic-resistant bacteria is illustrated by the example of MRSA-associated surgical wound infections. *Staph. aureus* is associated with 19 percent of all surgical wound infections, and 15 percent of all *Staph. aureus* is MRSA. Therefore, the hospital cost of MRSA-associated surgical wound infections is $50 million [$1.6 billion × 0.19 × 0.15 = $50 million]. Repeating this process for the five kinds of infections and the six different antibiotic-resistant bacteria produces an annual total of $661 million (1992) for hospital costs.

Using the estimate of Holmberg, Solomon and Blake (1987) that antibiotic resistance doubles the cost of nosocomial infections, the *minimum* extra cost of antibiotic-resistant bacteria in hospitals is $661 million annually (1992 dollars) and the *minimum* total cost of antibiotic-resistant bacteria in hospitals is $1.3 billion annually (1992 dollars). The actual hospital costs are bound to be much higher as this calculation considers only six species of bacteria, and in some cases considers strains of bacteria that are resistant to only one antibiotic and not other strains of the same bacteria that are resistant to other antibiotics. Further, the trends in antibiotic resistance indicate that the number of antibiotic-resistant infections is likely to be increasing rapidly. Finally, the OTA estimate considers only one factor among many that increase the costs of antibiotic-resistant bacteria; it ignores costs of other infections, costs of days of work lost, and post-hospital care, and other major costs. For these reasons, the OTA estimate of $1.3 billion must be considered a **minimum** estimate .

CONCLUSIONS

Twenty-five to 35 percent of all hospitalized patients receive antibiotics, which produces enormous pressure for the selection of antibiotic-resistant bacteria. The result of that pressure is increasing frequencies of antibiotic-resistant bacteria in hospitals: Some strains of vancomycin-resistant Enterococcus are now resistant to all FDA-approved antibiotics, and some strains of *Staphylococcus aureus*, a common cause of nosocomial infections, are resistant to all antibiotics except vancomycin. Many experts fear the emergence and spread of *Staph. aureus* strains resistant to all antibiotics, including vancomycin, which would pose a major health care crisis.

Two avenues are open to reduce the spread of antibiotic-resistant bacteria. One is infection control to reduce the rate of hospital infections, and the other is the reduction in the use of antibiotics to reduce selection pressures. While infection control programs have worked well in some institutions, similar programs have produced no positive results elsewhere. The mixed results indicate that more research into what makes systems work and why is needed to guide infection control efforts. Formularies, lists of drugs that are available for use in a hospital, were established to control drug costs, but they can be tied

TABLE 4-7: Costs of Stays in Hospital Associated with Antibiotic-Resistant Bacteria

	Surgical wound infection	Pneumonia	Bacteremia	Urinary tract infection	Other	Total
Total cost of nosocomial infections[a]	1.6	1.3	0.36	0.61	0.66	4.5
Staph. aureus	19%	20%	16%	2%	17%	
Methicillin resistant	15%	15%	15%	15%	15%	
Cost of MRSA[b]	50	40	10	1.8	20	122
Enterococcus	12%	2%	9%	16%	5%	
Vancomycin resistant	7.9%	7.9%	7.9%	7.9%	7.9%	
Cost of VRE[b]	20	2	2.6	10	2.4	37
Pseudomonas	8%	16%	3%	11%	6%	
Imipenem resistant	7.8%	16.9%	10.3%	6.9%	12.5%	
Cost of impenem-resistant pseudomonas[b]	10	40	1	4.6	5	61
Coagulase-negative Staphylococcus (CoNS)	14%	2%	31%	4%	14%	
Methicillin resistant	50%	50%	50%	50%	50%	
Cost of methicillin-resistant CoNS[b]	112	13	56	12	46	239
E. Coli	8%	4%	5%	25%	4%	
Ampicillin resistant	35%	35%	35%	35%	35%	
Cost of ampicillin-resistant *E. Coli*[b]	45	18	6	5	9	83
Enterobacter	7%	11%	4%	5%	4%	
Resistant	37%	37%	37%	37%	37%	
Cost of resistant enterobacter[b]	41	52	5	11	9.7	119
TOTAL COST[b]						661

[a] In billions of 1992 dollars.

[b] In billions of 1992 dollars.

NOTE: The costs were estimated by multiplying the total cost of nosocomial infections from a specific category (e.g., urinary tract infections) by the fraction of infections in that category caused by a specific organism (e.g., *E. coli*) and the fraction of the organism resistant to one specific antibiotic (e.g., ampicillin). The data from the fraction of infections caused by specific organisms and organisms resistant to a specific antibiotic were taken from the CDC/NNIS system. This calculation represents a minimum estimate of the costs of antibiotic resistant bacteria: it only accounts for charges in a hospital for nosocomial acquired infections due to six different antibiotic resistant species.

SOURCE: Office of Technology Assessment, 1995, based on data from the Centers for Disease Control, National Nosocomial Infections Surveillance (CDC/NNIS) System, Atlanta, GA.

to information about antibiotic susceptibility produced by the hospital microbiology laboratory to inform physicians' prescription decisions. Positive results have been reported in the few places this has been tried, but more evaluation will be necessary before it is widely adopted.

Surveillance systems are designed to collect and disseminate information to physicians and others about the presence and prevalence of antibiotic-resistant bacteria. They are common in hospitals, but far less common between and among hospitals and across larger geographical units. New Jersey has the only statewide system

in the country, and CDC is only now establishing a nationwide system for one kind of antibiotic-resistant bacterium. In addition, a number of privately supported surveillance systems collect data for pharmaceutical companies, but, understandably, those systems collect information for their clients rather than for general public health information. On the international level, WHONET collects data from over 100 institutions around the world. Chapter 1 discusses some features that could be built into a national surveillance system directed at antibiotic-resistant bacteria and offers an option for its implementation.

One estimate of the total costs associated with antibiotic-resistant bacteria had a range of $100 million to $30 billion annually, with most of the 300-fold range in cost coming from varying estimates of the value of a human life, and another estimate said that the costs could be up to $4 billion annually. OTA estimates the minimal extra hospital costs associated with five kinds of nosocomial infections caused by antibiotic-resistant bacteria to be $1.3 billion per year. The total costs would certainly be certainly higher when hospital costs of other antibiotic-resistant bacterial infections and non-hospital costs are considered.

REFERENCES

Ballow, C.H., and J.J. Schentag. 1992. Trends in antibiotic utilization and bacterial resistance. Report of the National Nosocomial Resistance Surveillance Group. *Diagnostic Microbiology and Infectious Disease 15*(Suppl. 2):37S–42S.

Burke, J.F. 1961. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery 50*:161–168.

Classen, D.C., R.S. Evans, S.L. Pestotnik, et al. 1992. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *New England Journal of Medicine 326*(5): 281–286.

Doebbeling, B.N., G.L. Stanley, C.T. Sheetz, et al. 1992. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *New England Journal of Medicine 327*(2): 88–93.

Eickoff, T.C. 1992. Antibiotics and nosocomial infections. In: J.V. Bennett, and P.S. Brachman (eds.). *Hospital Infections Third Edition*. Boston, MA. Little, Brown and Company.

Evans, R.S., and S.L. Pestotnik. 1993. Applications of medical informatics in antibiotic therapy. In: J.A. Poupard, L.R. Walsh, and B. Kelger (eds.) *Antimicrobial Susceptibility Testing: Critical Issues for the 90s*. New York, NY. Plenum Press, pp. 87–96.

Evans, R.S., S.L. Pestotnik, J.P. Burke, et al. 1990. Reducing the duration of prophylactic antibiotic use through computer monitoring of surgical patients. *DICP, The Annals of Pharmacotherapy 24*:351–354.

Evans, R.S., D.C. Classen, S.L. Pestotnik, et al. 1994. Improving empiric antibiotic selection using computer decision support. *Archives of Internal Medicine 154*(8):878–884.

Garner, J.S. 1993. The CDC hospital infection control practices advisory committee. *American Journal of Infection Control 21*(3):160–162.

Goldmann, D. and E. Larson. 1992. Hand-washing and nosocomial infections [editorial comment]. *New England Journal of Medicine 327*(2): 120–122.

Haley, R.W. 1991. Measuring the costs of nosocomial infections: Methods for estimating economic burden on the hospital. *American Journal of Medicine 91* (Suppl. 3B):32S–38S.

Haley, R.W. 1992. Cost-benefit analysis of infection control programs. In: J.V. Bennett and P.S. Brachman (eds.) *Hospital Infections Third Edition*, Boston, MA. Little, Brown and Company, pp. 507–532.

Haley, R.W., J.W. White, D.H. Culver, et al. 1987. The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. An empirical

determination from a nationally representative sample. *Journal of the American Medical Association 257*(12):1611–1614.

Haley, R.W., D.H. Culver, J.W. White, et al. 1985. The nationwide nosocomial infection rate: a new need for vital statistics. *American Journal of Epidemiology 121*(2):159–167.

Holmberg, S.D., S.L. Solomon, and P.A. Blake. 1987. Health and economic impacts of antimicrobial resistance. *Reviews of Infectious Diseases 9*(6)*:*1065–1078.

Institute of Medicine. 1992. *Microbial Threats to Health in the United States.* Washington D.C., National Academy Press.

Joint Commission on Accreditation of Healthcare Organizations. Feb. 1995. *IMSystem General Information*. Oak Terrace, IL, p. 15.

Jewell, M. 1994. Cost-containment using an outcome-based best practice model for the management of MRSA. *Journal of Chemotherapy VI*(Suppl. 2):35–39.

Kernodle, D.S., and A.B. Kaiser. 1990. In: Mandell, G.L., J.E. Bennett, and R. Dolin (eds.) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases.* New York, NY. Churchill Livingstone, Inc.

Kollef, M.H. 1994. Antibiotic use and antibiotic resistance in the intensive care unit: Are we curing or creating disease? *Heart and Lung 23*:363–367.

Kollef, M.H. 1994. The role of selective digestive tract decontamination on mortality and respiratory tract infections: A meta-analysis. *Chest 105:*1101–1108.

Leape, L.L. 1990. Practice guidelines and standards: an overview. *16 Quality Review Bulletin*, pp. 42–49.

Loeb, J.M., D.S. O'Leary. 1995. A call for collaboration in performance measurement. (From the Joint Commission on Accreditation of Healthcare Organizations). *Journal of the American Medical Association 273*(18):1405.

Lonks, J.R., Durkin, M.R., Meyerhoff, A.N., et al. 1995. Meningitis due to ceftriaxone-resistant *Streptococcus pneumoniae*. *New England Journal of Medicine 332*:893–894.

Loulergue, J., A. Audurier, J.M. DeLarbre, et al. 1994. Changes in microbial ecology and use of cloxacillin. *Journal of Hospital Infection 27*(4):275–283.

Mandell, G.L., J.E. Bennett, and R. Dolin. 1990. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases.* New York, NY. Churchill Livingstone, Inc.

Mandell, G.L., and M.A. Sande. 1990. Antimicrobial agents: penicillins, cephalosporins, and other beta-lactam antibiotics. In: A.G Gilman, T.W. Rall, A.S. Nies, et al. (eds.) *Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eighth Edition.* New York, NY. Pergamon Press, pp. 1065–1097.

Martin, M.A. 1994. Methicillin-resistant *Staphylococcus aureus:* the persistent resistant nosocomial pathogen. *Current Clinical Topics in Infectious Diseases 14*:170–91.

Martone, W.J., W.R. Jarvis, D.H. Culver, et al. 1992. Incidence and nature of endemic and epidemic nosocomial infections. In: J.V. Bennett, and P.S. Brachman (eds.) *Hospital Infections Third Edition.* Boston, MA. Little, Brown and Company, pp. 577–596.

McGowan, Jr., J.F. 1994. Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance? *Infection Control and Hospital Epidemiology 15*(7):478–483.

Meyers, K., Chief of Infectious Diseases and Hospital Epidemiologist, Baptist Medical Center. Feb. 21, 1995. Personal communication.

Murray-Leisure, K.A., Geib, S., Graceley, D. et al. 1990. Control of epidemic methicillin-resistant *Staphylococcus aureus*. *Infection Control and Hospital Epidemiology 11*(7):343–350.

National Foundation for Infectious Disease. 1990. Press release at Interscience Conference on Antimicrobial Agents and Chemotherapy. Reported in D. North. 1993.

National Health Lawyers Association Colloquy. 1995. *Legal Issues Related to Clinical Practice Guidelines. vol. 47.*

Noble, W.C., Z. Virani, and R.G. Cree. 1992. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS-Microbiol-Lett. 72*(2): 195–198.

North, D. 1993. Controlling the Costs of Antibiotic Resistance. *Clinical Therapeutics 15*(Suppl. A):3–11.

Phelps, C.E. 1989. Bug/drug resistance. Sometimes less is more. *Medical Care 27*:194–203.

Rosdahl, V.T., and A.M. Knudson. 1991. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology 12*(2):83–88.

Rosendal, K., O. Jessen, M.W. Bentzon, et al. 1977. Antibiotic policy and spread of *Staphylococcus Aureus* strains in Danish hospitals, 1969–1974. *Acta Pathologica et Microbiologica. Scandinavica (Sect. B) 85*:143–152.

Rotter, M. 1988. Are models useful for testing hand antiseptics? *Journal of Hospital Infections 11* (Suppl. A):236–243.

Sanford, J.P. 1992. Forward. In: J.V. Bennett, and P.S. Brachman (eds.) *Hospital Infections Third Edition.* Boston, MA. Little, Brown and Company.

Scott, L. June 13, 1994. Restraint on use of antibiotics urged. *Modern Healthcare,* p. 47.

Shanz, S.J. Fall 1993. The emerging status of practice parameters. *7 Medical Staff Counsel 31*.

Siegel, J.D., G.H. McCracken Jr., N. Threlkeld, et al. 1980. Single-dose penicillin prophylaxis against neonatal group B streptococcal infections. A controlled trial in 18,738 newborn infants. *New England Journal of Medicine 303*:769–775.

Silber, J.L., S.M. Paul, G. Crane, et al. 1994. Influence of hospital antibiotic policy and usage on the incidence of vancomycin-resistant enterococcal (VRE) bacteremia. Abstract. *Infection Control and Hospital Epidemiology 15*(4):32.

Simmons, B., J. Bryant, K. Neiman, et al. 1990. The Role of Handwashing in Prevention of Endemic Intensive Care Unit Infections. *Infection Control and Hospital Epidemiology 11*(11):589–594.

Spink, W.W., and V. Ferris. 1945. Quantitative action of penicillin inhibitor from penicillin-resistant strains of staphylococci. *Science 102*:221.

St. Paul Fire & Marine Insurance Co. 1995. *1994 Annual report to policyholders,* pp. 4–5.

Strausbaugh, L.J., C. Jacobson, D.L. Sewell, et al. 1992. Antimicrobial therapy for methicillin-resistant *Staphylococcus aureus* colonization in residents and staff of a veterans affairs nursing home care unit. *Infection Control and Hospital Epidemiology 13*(3):151–159.

The Medical Letter on Drugs and Therapeutics. 1994. *Handbook of Antimicrobial Therapy.* New Rochelle, NY. The Medical Letter, Inc.

U.S. Congress, Office of Technology Assessment. September 1995. *Bringing Health Care Online: The Role of Information Technologies,* Washington, DC. U.S. Government Printing Office.

U.S. Department of Public Health, Public Health Service, Agency for Health Care Policy and Research. July 1994. *Clinical Practice Guideline Number 12: Otitis Media with Effusion in Young Children.* AHCPR Pub. No. 94-0622. Rockville, MD.

U.S. Department of Public Health, Public Health Service, Centers for Disease Control. 1995. *Morbidity and Mortality Weekly Report 44*:27.

Waldvogel, F.A. 1995. *Staphylococcus aureus* (including toxic shock syndrome). In: G.L. Mandell, J.E. Bennett, and R. Dolin (eds.) *Mandel, Douglas and Bennett's Principles and Practice of Infectious Diseases Fourth edition*. New York, NY. Churchill Livingstone, Inc., p. 1757.

Wenzel, R.P. 1992. Preoperative antibiotic prophylaxis. *New England Journal of Medicine 326*(5):337–339.

Westh, H., J.O. Jarlov, H. Kjersem, et al. 1992. The disappearance of multiresistant *Staphylococcus aureus* in Denmark: changes in strains of the 83A complex between 1969 and 1989. *Clinical Infectious Diseases 14*(6):1186–1194.

Willy, M.E., G.L. Dhillon, N.L. Loewen, et al. 1990. Adverse exposures and universal precautions practices among a group of highly exposed health professionals. *Infection Control and Hospital Epidemiology 11*(7):351–356.

Yu, V.L., G.P. Stoehr, R.C. Starling, et al.. 1991. Empiric antibiotic selection by physicians: evaluation of reasoning strategies. *American Journal of the Medical Sciences 301*:165–172.

Antibiotic Development 5

The fact that U.S. Food and Drug Administration (FDA) approved no new antibiotics in 1994 has led to fear that there are no new ideas for antibiotics or that there are insufficient financial incentives for new antibiotic development. Even the information that 13 new antibiotics are currently awaiting FDA approval, and that two-thirds of the 53 antibiotics developed by drug companies since 1960 received FDA approval after 1980 (*Modern Healthcare*, 1994) must be tempered by additional information. The 13 antibiotics awaiting approval are not "new" in terms of new mechanisms of action. They are derivatives or new applications or formulations of antibiotics already on the market.

As shown in figure 5-1 (and discussed below) several years elapse between the discovery of a chemical with antibiotic activity and its reaching the market. The scarcity or abundance of new antibiotics is dependent on many factors, some of which are described in this chapter, but some of the decisions necessary for the appearance of new antibiotics in 1995 were made years ago.

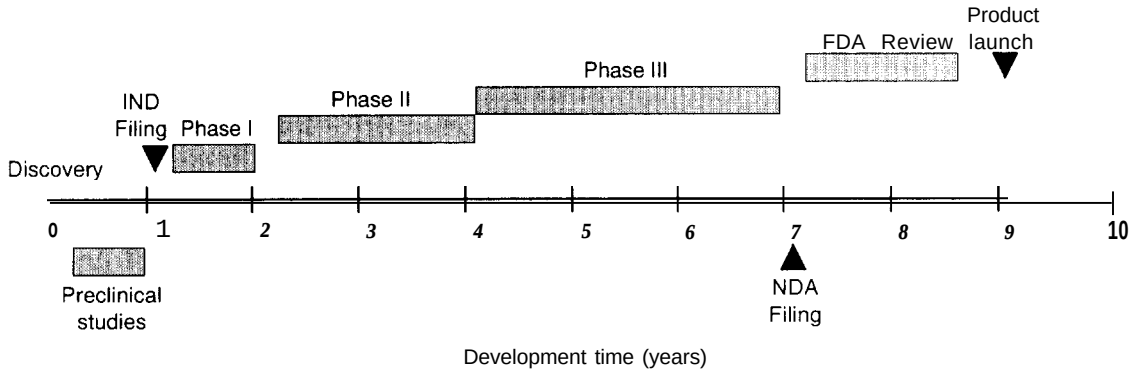
This chapter reviews general considerations in the development of new antibiotics and describes some antibiotics that are now in use and how researchers are attempting to modify them to extend their usefulness. It also discusses the search for new antibiotics using new chemical and molecular biology knowledge and techniques as well as the search for new antibiotics in biological materials not formerly examined. It also reviews briefly some aspects of drug development and approval (those issues are covered in greater depth in OTA's 1993 report *Pharmaceutical R&D: Risks, Costs, and Rewards).*

DESIGNING NEW ANTIBIOTICS

Development of almost any drug is a matter of science and serendipity, and antibiotics are no different. Traditional methods, like screening of soil and biological samples—"panning" for compounds—have been partly replaced by computerized modeling, recombinant DNA technologies, new methods of chemical synthesis, and other advances (Levy 1992, p. 39). Nevertheless, looking for antibiotic activity in biological materials as exotic as frogs and the silk glands of moths is a part of current research.

No matter how chemicals with antibiotic properties are derived, they must still be evaluated in the microbiology laboratory, laboratory animals, and ultimately, humans. "Preclinical studies" are tests for efficacy and toxicity in laboratory animals, and "phases I, II, and III" are

FIGURE 5-1: Approximate Timeline for the Development of a New Antibiotic



NOTE: IND = Investigational new drug: NDA = new drug application.

SOURCE: Gootz, 1990.

clinical trials in humans, with phase I being trials to establish the safety of the drug and phases II and III to establish efficacy (figure **5-1).**

The creation of a new idea is the critical starting point for much research, and probably every company tries methods to encourage creativity. Once an idea is developed, the company can speed up the pre-clinical research by pouring additional resources into it, increasing the numbers of scientists committed to the project, and providing more and better equipment.

▮ Toxicity

Toxicity tests in animals and humans identify what side effects may occur; but the occurrence of such effects does not mean that the developer will drop the drug or that FDA will not approve it. It does mean that the toxicity will be weighed against the benefits in deciding what uses will be sought by the developer and what uses will be permitted by FDA. For instance, greater toxicity would be acceptable in an antibiotic to treat vancomycin-resistant Enterococcus (VRE), for which there are few or no available antibiotics, than in one intended for routine use against respiratory infections for which there are many available antibiotics.

Most antibiotics inhibit or kill bacteria while remaining relatively non-toxic to humans because of differences between the structures and metabolic characteristics of bacterial and animal cells (see chapter 2). One major difference is the presence of the cell wall that surrounds the plasma membrane in bacteria. Cell walls are missing from animal cells, and many antibiotics kill bacteria by interfering with cell wall synthesis.

Despite their generally low toxicity, antibiotics can cause allergic reactions and other side effects. Penicillin can be allergenic, and vancomycin can cause hearing loss and kidney damage. Many promising new compounds that inhibit or kill bacteria in the test tube are not useful as drugs because of allergenic or other toxic side effects.

▮ Efficacy

The Infectious Disease Society of America, a professional medical organization, under contract to FDA, developed guidelines for clinical trials that outline the minimal acceptable information to be submitted to FDA. Because antibiotics are available for the treatment of almost all bacterial diseases, it is unethical to test a new antibiotic by comparison with a placebo. Instead, one half of the patient population is given the standard antibiotic treatment, and the other half is given the new antibiotic. This comparison of

efficacies necessarily requires more patients than if the antibiotic were evaluated against no treatment or a placebo. If the new antibiotic is equal to or more effective in treating the disease than the standard treatment, FDA will approve its use. Even if it is not quite so effective, FDA will approve the new antibiotic if it has lower toxicity than the standard to which it is compared.

FDA will consider the results of foreign trials when the makeup of the test population in the foreign country approximates the U.S. population, the distribution of antibiotic-resistant bacteria in the foreign country is about the same as in the United States, and the disease is caused by the same bacteria in the other country and in the United States. The Office of Technology Assessment (OTA) did not investigate how often, if ever, FDA has decided not to consider a foreign trial, but there appears to be some room for disagreement between a manufacturer and FDA about how closely the foreign conditions approach those in the United States. On the other hand, an FDA official stated that multi-national companies have done one trial in a European country and one in the United States, combined the results, and obtained approval for the new drug in both countries, and that FDA will make approval decisions based solely on foreign studies (FDA, 1995).

The time necessary for FDA review has decreased in the last few years. In the early 1990s, FDA took an average of 25 months to act on a New Drug Application (NDA). Through "The Prescription Drug User Fee Act of 1992 (P.L. 102-571)," Congress increased funds for FDA to staff and run the review process. That law requires that each manufacturer pay an annual fee based on the number of the company's drugs that are in use and the number of its manufacturing plants. In addition, manufacturers may pay a fee at the time of submission of an NDA. These fees are used to hire additional reviewers at FDA to speed up the review process, not to speed up the review of the particular NDA. Since the Act's implementation, the average time for FDA drug approval in 1994 had dropped to 19 months.

The time line on figure 5-1 is an approximation; some drugs move more quickly through the trials, and some move more slowly. More frequently, a drug fails some critical test and must be abandoned. Such hurdles have always been present. Scaling-up production of a drug from the small quantities needed for initial testing to the large quantities needed for phase III clinical testing and manufacture can also be significant hurdles in getting a new drug to market (box 5-1).

FDA regulations allow for an accelerated review process when a candidate drug is a possible treatment for a life-threatening disease (such as an antibiotic for use against VRE). FDA officials can meet with the drug sponsors at the end of the phase I trial and design a phase II trial that will be sufficient to make a decision about approval of the drug. Moreover, drugs that are entered into accelerated review go to the "head of the line" at all stages of the review process.

A company seeking approval to market an antibiotic for use against diseases caused by antibiotic-resistant bacteria must demonstrate efficacy against particular bacteria-disease combinations. For instance, an antibiotic effective

BOX 5-1: Quantities of Drugs Needed at Different Stages of Development

0.01 g-10 g: Discovery (performs initial bench-level discovery, creation, or isolation of the new entity).

10 g-100 g: Chemical process research (identifies possible ways to make the entity on a larger scale).

1,000 g-100,000 g: Chemical process development (a collaboration between research and development programs (R&D) and manufacturing; scales up manufacture for toxicology and clinical research; makes the process useful for manufacturing).

100,000 g-1,000,000 g: Manufacture (scales up once again to make the entity in commercial amounts).

SOURCE: Bristol-Meyers Squibb, 1995.

against VRE in laboratory tests would have to be shown effective against VRE-caused endocarditis to be marketed for that use, and it would also have to be shown effective against VRE-caused bacteremia to be marketed for use against that indication. This raises problems because the number of such diseases is relatively small, making it difficult to obtain as many cases for a clinical trial as are commonly required. According to a U.S. FDA official, however, the agency could adjust the number of cases required for the trial of an antibiotic for use against particular diseases caused by particular antibiotic-resistant bacteria.

ANTIBIOTICS IN CURRENT CLINICAL USE

Table 5-1 is a listing of the actions of antibiotics, a sampling of antibiotics that display those actions, and the development or use status of the antibiotics. Currently, research and development efforts are in place that seek to improve currently used antibiotics.

Sulfonamides[1]

The sulfonamides are synthetic, not of natural origin, and are properly called "antimicrobials" and not antibiotics. They are included here because they were the first antibacterial drugs that were not overtly toxic to humans, and their chemical modifications foreshadowed much of the work to improve natural antibiotics.

In 1936, a year after German researchers reported that Prontosil (the first sulfonamide) cured bacterial diseases, British researchers set out to improve upon its usefulness (Colebrook and Kenny, 1936). The British researchers' plans were based on the results of studies by French investigators, who noted that the antibacterial effects of compounds like Prontosil were lost when some parts of the chemical were removed, but that removal of other substituents had no effect on antibacterial properties in mice. They concluded that a metabolic product, para-aminobenzenesulfonamide, was responsible for the activity of Prontosil, and that the full structure of the parent compound was not necessary for bacterial killing. The involvement of researchers from three different countries in this research points to the international flavor of antibiotic research from its very beginning.

The British researchers tested a dozen sulfonamide analogues for antibiotic activity, but, practically, their most important discovery was that para-aminobenzenesulfonamide was well tolerated when injected subcutaneously and that it could be given orally. Prontosil, on the other hand, was biologically active only when given by injection (Buttle et al., 1936; Mandell and Sande, 1990). This finding was another harbinger of research directions with antibiotics; low toxicity and ease of administration increased the acceptability of an antibiotic and reduced the medical care costs associated with it.

If bacteria were passive when faced with antibacterials, the sulfonamides would have remained potent therapy. Bacteria are not passive. Through mutation and selection, they become resistant to antibiotics. This sets up the struggle between antibiotic developers and bacteria—the biological war.

Sulfonamides inhibit one step in the bacterial synthesis of folic acid. Humans and other mammals do not synthesize folic acid; they obtain it from food. Hence, sulfonamides have no effect on mammalian cells. When, by the early 1960s, many bacteria had developed resistance to the sulfonamides, researchers postulated that the antimicrobial action of sulfonamides might be augmented by the co-administration of trimethoprim, which blocks another step in folic acid synthesis (Bushby and Hitchings, 1968). Blocking two sequential enzymes on the bacterial biosynthetic pathway of a vital nutrient (such as folic acid) was expected to act synergistically. The reasoning proved correct, and bacteria resistant to sulfonamide were inhibited by the sulfonamide/trimethoprim formulation. The preparation is still used widely.

[1] NOTE: An OTA mention of products and companies does not imply any endorsement, and products and companies are included only as examples.

Action	Family/Class	Example(s)	Source	Status
Antibiotics that inhibit cell wall synthesis	Beta-lactams			
	Natural penicillins	Penicillin G	*Penicillin notatum*	Used since 1940s
	Semi-synthetic penicillins	Methicillin	Semi-synthetic penicillin derivatives	In use since 1960s; among the most widely prescribed antimicrobials
		Piperacillin		
	Cephalosporins	Cephalexin	*C. acremonium*	Widely used class of antibiotics
	Carbapenems	Imipenem	Derived from thienamycin, a compound produced by *Streptomyces cattleya*	In use; wide spectrum (active against many species of bacteria including cephalosporin-resistant Enterobacteriaceae)
	Monobactams	Aztreonam	Derived from a compound produced by *Chromobacterium violaceum*	In use; tolerated by patients with penicillin allergies; spectrum limited to aerobic gram-negative bacteria
	Penicillinase inhibitors	Clavulanate potassium (used clinically with amoxicillin or ticarcillin)	*Streptomyces clavuligerius*	Used since 1970s; clavulanate combinations used for wide range of disorders
		Sulbactam (used with ampicillin)	Semi-synthetic penicillin derivative	Similar to amoxicillin/clavulanate
		Tazobactam sodium (used clinically with piperacilllin)	Semi-synthetic penicillin derivative	Tazobactam/piperacillin effective against intra-abdominal infections
	Vancomycin	Vancomycin	*Strep. orientalis*	Introduced in 1956; used against staphylococcal and enterococcal infections
	Teicoplanin	Teicoplanin	*Actinoplanes teichomyceticus*	Experimental in the U.S., available for compassionate use
	Vancomycin derivatives with catalytic activity		Semi-synthetic	Experimental

(continued)

TABLE 5-1: Antibiotics in Use and Under Development (Cont'd.)

Action	Family/Class	Example(s)	Source	Status
Antibiotics that increase membrane permeability	Peptides			
	Bactericidal/Permeability Increasing Protein (BPI)		Mammalian cells	Experimental
	Magainins		African clawed frog	Experimental
	Cecropins		Silk moth, other insects, mammals	Experimental
	Defencins		Mammalian cells	Experimental
	Steroids		Dogfish sharks	Experimental
Metabolic interference	Sulfonamides	Sulfamethoxazole	Azo dyes	In use since 1930s; first antimicrobial agent used in man
	Trimethoprim	Trimethoprim	Synthetic	Synthesized in 1968, commonly used together with sulfonamides
Protein synthesis inhibitors	Aminoglycosides	Streptomycin Kanamycin Tobramycin Gentamicin	*Streptomyces griseus* *Streptomyces kanamyceticus* *Streptomyces tenebrarius* *Micromonspora purpurea* and *echinospora*	In use since 1940s; important class of antibiotics
	Fusidanes	Fucidin	Sodium salt of fusidic acid, derived from the fungus *Fusidium coccineum*	In clinical use since 1962, but not available in US (except through compassionate release); active against some strains of methicillin-resistant *Staph. aureus* (MRSA)
	Tetracyclines	Chlortetracycline Oxytetracycline Minocycline Doxycycline	*Streptomyces aurofaciens* *Streptomyces rimosus* Semi-synthetic derivative Semi-synthetic derivative	First introduced in 1948, found by screening soil samples for antibacterial activity

(continued)

TABLE 5-1: Antibiotics in Use and Under Development (Cont'd.)

Action	Family/Class	Example(s)	Source	Status
	Chloramphenicol	Chloramphenicol	*Streptomyces venezuelae*	First introduced in 1949, currently second line antibiotic because of side effect of aplastic anemia
	Macrolides Azalides	Erythromycin Azithromycin	*Streptomyces erythreus* semi-synthetic derivative of erythromycin	Discovered in 1952 Usage began in 1992
	Lincosamides	Clindamycin	Semi-synthetic derivative of lincomycin derived from *Streptomyces lincolnensis*	Available since the mid 1960s; active against aerobic bacteria
	Mupirocin	Mupirocin	*Pseudomonas fluorescens*	Introduced in the mid 1980s; topical antibiotic
Interference with RNA synthesis	Rifamycins	Rifampin	*Streptomyces mediterranei*	First isolated in 1957, important tuberculosis drug
Toxic effect through DNA binding	Nitroimidazoles	Metronidazole	Synthetic	Introduced in 1959, active against anaerobes such as *B. fragilis*
Block DNA replication or RNA transcription	Antisense nucleotides		Laboratory	Experimental
Interfere with DNA replication	Quinolones Fluoroquinolones	Nalidixic acid Ciprofloxacin, Ofloxacin	Semi-synthetic	First identified in 1962 Usage began in 1980s; some of the most widely used antibiotics
Anti-tuberculosis drugs		Isoniazid (INH) Pyrazinamide (PZA)	Synthetic Synthetic	Shown to be effective in 1952 Important tuberculosis drug since 1980
		Ethambutanol	Synthetic	Important tuberculosis drug since 1974
Decoy receptors	Carbohydrates		Laboratory	Experimental

SOURCE: OTA, compiled from G.L. Mandell, J.E. Bennett and R. Dolin (eds.) *Mandell, Douglas & Bennett's Principles & Practice of Infectious Diseases*. Churchill Livingstone: New York, NY, 1995; and A.G. Gilman, T.W. Rall, A.S. Nies, et al. (eds.) *The Pharmacological Basis of Therapeutics*. Pergamon Press; New York, NY, 1990.

Penicillins and Clavulanic Acid

Penicillin was the first true antibiotic. Its action involves binding to penicillin-binding proteins which are enzymes necessary for the synthesis of the bacterial cell wall, inhibiting those enzymes, which leads to the death of the cell, and uncovering or activating other enzymes that cause the bacterial cell to burst. Shortly after penicillin's introduction, resistant micro-organisms began to appear. By the mid-1940s, the enzyme penicillinase or β-lactamase, which degrades penicillin so that it has no effect on bacteria, had been isolated from a bacterium that was not specifically identified, and soon after, scientists found it was present in other bacteria such as *Staphylococcus aureus*. As early as 1948, 50 percent of *S. aureus* in hospitals were resistant to penicillin, rising to 80 percent in 1957 (Gootz, 1990).

Semi-synthetic Penicillins

Semi-synthetic penicillins—methicillin, nafcillin, and cloxacillin—are the product of searches for penicillins that could escape the action of penicillinase. They were made possible by the large-scale production of a part of the penicillin molecule, called 6-aminopenicillanic acid, to which chemists could add different chemical substitutions. These penicillins resist the degrading action of penicillinases, and they found immediate application in treating some penicillin-resistant bacteria. The extremely low toxicity of penicillin has fueled efforts to continue development of this antibiotic.

Penicillinase Inhibitors

Molds of the genus Streptomyces produce chemical compounds that "suicidally" tie up penicillinases. When administered with penicillins, the inhibitors bind the penicillinases, leaving the unbound penicillin free to kill bacteria (Reading and Cole, 1977). By the early 1970s, olivanic acid, produced by *Streptomyces olivaceus*, had proved a successful penicillinase inhibitor, and it was used with ampicillin and amoxicillin in treating *S. aureus* and *Klebsiella pneumonia*, both Gram-positive bacteria, but it was unable to penetrate the Gram-negative bacterial cell wall.[2] Clavulanic acid, from *Streptomyces clavuligerus*, proved more effective than the olivanic acids, and it extended the spectrum of penicillinase activity to Gram-negative bacteria. Amoxicillin/clavulanic acid is the mainstay of treatment for otitis media in children caused by *Hemophilus influenzae* and *Branhamella catarrhalis*.

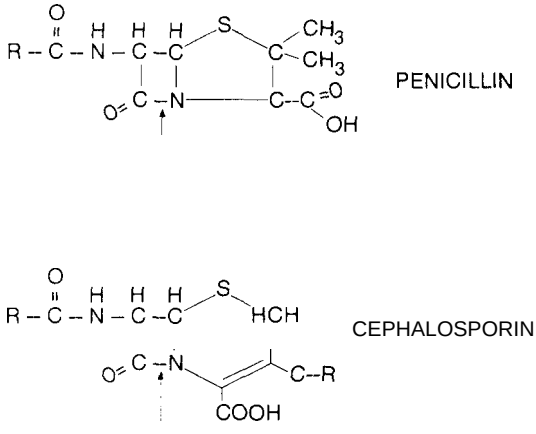
The success of the penicillin/clavulanic acid combination suggested that semi-synthetic penicillins—while promising as single-agent therapy—might not be the only solution to the problem of antibiotic resistance. More importantly, perhaps, the notion of identifying and attacking a specific bacterial target responsible for resistance (in this case, penicillinases) became a principle of antibiotic research.

Other Beta-Lactam Antibiotics

The cephalosporins (see figure 5-2) share a similar chemical structure (the beta-lactam ring) and similar mechanisms of action (inhibition of synthesis of the bacterial cell wall) with penicillin. Cephalosporin antibiotics were first isolated from the organism *Cephalosporium acremonium* in 1948 from the sea near a sewer outlet off the Sardinian coast (reviewed in Mandell and Sande, 1990). Chemists have modified the structure of the antibiotics and produced semisynthetic antibiotics with increased antimicrobial activity. The resulting so-called "third generation" cephalosporins, including ceftriaxone and ceftazidime, are widely used. Imipenem, yet another β-lactam antibiotic, is a chemical derivative of a compound first isolated from the organism *Streptomyces catleya*; it is the broadest-spectrum antibiotic commercially available (see Emori and Gaynes, 1993).

[2] Some bacteria take up a stain, called the Gram stain, and some do not. The difference depends on the structure of the cell wall in the two kinds of bacteria, and the permeability of the two kinds of bacteria differ as a result of the difference in the cell walls.

FIGURE 5-2: Core structure of penicillins and cephalosporins



NOTE The R groups specify the particular antibiotic; arrows indicate the bond broken during function and during inactivation by b-lactamases

SOURCE: Frankel, 1995

▮ Vancomycin

Vancomycin is a naturally occurring glycopeptide [a protein (peptide) molecule with attached sugars (glyco-)] antibiotic that blocks synthesis of the bacterial cell wall. However, vancomycin inhibits the synthesis of the bacterial cell wall by binding to the peptidoglycan (cell-wall) precursor, a very different mechanism from that used by the penicillins, and it does not have the beta-lactam ring structure of penicillins. Vancomycin has become clinically important because it is sometimes the only drug that can be used to treat MRSA (methicillin-resistant S. *aureus)* infections, an increasingly prevalent pathogen in hospitals (see chapter 4).

Teicoplanin, a related glycopeptide antibiotic, is widely used in Europe, but is available only as an investigational drug in the United States. It is potentially an effective alternative to vancomy - cin; it requires less frequent dosing, and it is less toxic. It is not likely to be successful in treating bacteria resistant to vancomycin because bacteria resistant to vancomycin are usually resistant to teicoplanin as well (Fekety, 1995).

ANTIBIOTICS THAT INHIBIT OR BLOCK DNA REPLICATION OR PROTEIN SYNTHESIS

While the general features of DNA replication and protein synthesis are common to bacterial and animal cells, subtle differences exist, and some antibiotics inhibit bacterial DNA replication or protein synthesis without harming the analogous processes in animal cells.

▮ DNA Synthesis—Ciprofloxacin, Other Quinolones, and Fluoroquinolones

The synthetic antibiotic ciprofloxacin has become one of the most widely prescribed antibiotics since its introduction in 1987 (Frieden and Mangi, 1990). Ciprofloxacin, other quinolones, and fluoroquinolones work by inhibiting the action of a bacterial enzyme necessary for DNA synthesis ("DNA gyrase"). Ciprofloxacin is derived from nalidixic acid, an antibiotic discovered 15 years earlier, but never widely used. Therefore, ciprofloxacin had a substantially "new" mechanism of' action. It is not known whether quinolones bind to animal cell DNA gyrase, but these antibiotics are relatively nontoxic.

Although resistance to ciprofloxacin occurs at rates 100- to 1,000-times slower than resistance to nalidixic acid (Hooper and Wolf son. 1989), many strains of bacteria became resistant to ciprofloxacin over a period of three years (see table 5-2). This experience shows that resistance can develop rapidly even when the mechanism of action is substantially "new. "

Ciprofloxacin and other quinolones are popular because they are effective against bacteria that have developed resistance to other antibiotics and because they can be taken orally rather than requiring parenteral administration (through injection or intravenously). Oral ciprofloxacin is equally or more effective than many parenteral antibiotics, and oral administration costs less, and can reduce or eliminate hospital stays.

TABLE 5-2: Resistance to Ciprofloxacin, 1988-1990

Organism	% Resistant		
	1988	1989	1990
Acinetobacter anitratus	0	34	40
Enterococcus (various species)	8	25	35
Methicillin-resistant *Staphylococcus aureus*	—	—	85
Pseudomonas aeruginosa	9	35	45
Staphylococcus aureus	6	10	20

SOURCE: Adapted from Husain, 1991.

RNA Synthesis—Rifampin

The first step in protein synthesis is the transcription of information in DNA into RNA (see chapter 2). Rifampin binds to bacterial RNA polymerase, inhibits bacterial RNA synthesis, and does not bind to animal cell RNA polymerase. Its principal use is in the treatment of tuberculosis (TB).

Protein Synthesis—Streptomycin and Other Aminoglycosides

The inactivity of penicillin G against Gram-negative bacteria led scientists to search for antibiotics with activity against those organisms. The 1944 discovery of streptomycin from a strain of the bacterium *Streptomyces griseus* was followed by discovery of related compounds such as neomycin, kanamycin, and gentamicin from other bacteria in later years. This family of antibiotics, the aminoglycosides, inhibits bacterial protein synthesis by binding to the small subunit of the bacterial ribosome, which differs from the corresponding subunit of the animal ribosome (see chapter 2). Aminoglycoside inhibition of protein synthesis is irreversible and lethal to the bacteria.

Other antibiotics that inhibit protein synthesis are the macrolides, such as erythromycin, clindamycin, and chloramphenicol, which bind to the large subunit of the bacterial ribosome. They inhibit bacterial growth, but they do not kill the bacteria. (Chloramphenicol is now seldom used in medicine because of adverse side effects.) Tetracyclines, which are widely used in medicine, veterinary medicine, and animal husbandry (see chapter 7), are also inhibitors of protein synthesis with broad activity spectra. They, like chloramphenicol, are bacteriostatic rather than bactericidal.

DEVELOPMENT OF NEW ANTIBIOTICS FROM OLD

The development of semisynthetic penicillins and ciprofloxacin from nalidixic acid has demonstrated the usefulness of modifying existing antibiotics so they are active against resistant strains of bacteria. Modifications can reduce toxicity, make the antibiotic resistant to degrading enzymes, or improve penetration into bacterial cells.

Frankel (1995) contacted a number of large, established pharmaceutical companies and a number of smaller, startup or beyond, biotechnology firms and asked about their research and development programs in antibiotics. The section that follows is based on his report. It is an overview and should not be taken as exhaustive because not all firms were contacted, and not all firms were willing to discuss their research and development programs in antibiotics.

Streptogramins

Rhone-Poulenc Rorer (1995) announced that one of its antibiotics, now in phase III clinical trials, is effective against antibiotic-resistant bacteria, including some strains of VRE (*Journal of Antimicrobial Chemotherapy*, 1992). The antibiotic is currently available from the company in an FDA-reviewed program, and it is usually shipped within 24 hours of request.

This drug is a combination of two semisynthetic derivatives of streptogramin, an antibiotic from *Streptomyces pristinaespiralis*. One such antibiotic, pristinamycin, has been available in Europe for many years as an oral antistaphylococcal antibiotic. It inhibits protein synthesis by affecting ribosome function, but was never widely used, partially because it cannot be

made in an injectable form due to low water solubility. The new derivatives of pristinamycin—quinupristin/dalfopristin (used in combination)—are injectable.

Tetracycline Analogs

The first clinically useful tetracycline, chlortetracycline, was introduced in 1948. It was isolated from the micro-organism *Streptomyces aurofaciens* and was discovered after screening samples of Missouri farm soil (Levy, 1981). Following this discovery, other researchers identified more tetracyclines by further screening of soil micro-organisms or by synthesis in laboratories. As with the penicillins, manipulation of the tetracycline molecule has brought different spectrums and properties of antibiotic activity. While all of the tetracyclines now used in the United States are generally considered broad-spectrum agents, bacterial resistance to this family of agents is widespread.

"Active efflux," which transports tetracyclines out of the bacteria, is a major mechanism of bacterial resistance. Since its description (Levy, 1981), it has also been shown to be a mechanism of resistance to several other antibiotics including chloramphenicol, fluoroquinolones, erythromycin, and ß-lactams (Nikaido, 1994), and it is present in both Gram-positive and Gram-negative bacteria. Nikaido (1994) reviews evidence about permeability barriers to antibiotic entry into bacteria and active efflux, which can bestow resistance to many antibiotics, and states that, "It will be a major challenge for the pharmaceutical industry to produce compounds that are able to overcome mechanisms of this type."

Such research is underway. Nelson et al. (1993) tested 30 tetracycline analogues and identified two chemical substitutions that block active efflux. Subsequently, Nelson et al. (1994) determined the part of the tetracycline molecule that is essential for its antibacterial activity and which substitutions inhibit efflux. This information may increase the usefulness of tetracycline, an old antibiotic.

Minocycline, the last tetracycline to reach the market, was introduced in the 1970s, and it was the starting point for researchers who took another look at the tetracyclines in the late 1980s. This new tetracycline research program, a multidisciplinary effort by chemists, molecular biologists, biochemists and microbiologists, has produced the semisynthetic glycylcycline antibiotics. These are active against both Gram-positive and Gram-negative bacteria and evade resistance mediated by six of the known mechanisms of tetracycline resistance. Researchers are continuing to modify the glycylcyclines to optimize their antibacterial properties (Bergeron et al., 1994; Sum, Lee, Peterson et al., 1994), and have recently introduced modifications that may lead to the production of "later-generation" glycylcyclines (Sum, Lee, and Tally, 1994). When and whether they will reach clinical application is unknown.

Dual-Action Cephalosporins

One approach to evading bacterial resistance to cephalosporins or quinolones is to chemically couple the two to produce conjugates that have a dual mechanism of action (hence the name "dual-action" cephalosporins), reflecting the actions of both the ß-lactam, cephalosporin, and quinolone components.

The first of these conjugates, as reported by Georgopapdakau et al. (1989), was found to act initially as a cephalosporin by binding to appropriate penicillin-binding proteins, and then to inhibit DNA replication, as would be expected from the quinolone function. Some conjugates appeared to act primarily as cephalosporins, while others acted primarily as quinolones (Georgopapdakau and Bertasso, 1993). The pharmaceutical company that sponsored Georgopapdakau's work is no longer supporting research in dual-action cephalosporins, but such research is reportedly continuing in at least one other company.

Vancomycin Research

Vancomycin is the antibiotic of last resort in some specific situations, and it is a popular one, accounting for a quarter of the budget for antibiotics in some hospitals. The appearance of some strains of VRE that are resistant to all antibiotics[3] leaves physicians with no currently approved antibiotic treatment for infections caused by those organisms. Intravenous vancomycin is the first choice for the antibiotic treatment of MRSA, and the probably inevitable appearance of vancomycin-resistant MRSA will leave physicians with no marketed antibiotic effective against that serious nosocomial infection.

Currently, however, some strains of MRSA are reportedly susceptible to other antibiotics: Novobiocin, which is available only in oral form, is active against many strains of MRSA. Minocycline (a tetracycline) has been used in successful treatment of a few cases of endocarditis caused by MRSA. Most isolates of MRSA are susceptible to fusicid acid. Used in combination with other antibiotics, fusicid acid has been part of successful therapy for a variety of MRSA-caused diseases, but the role of fusicid acid is not entirely clear. Emergence of resistance to all of these antibiotics has been reported, and it is especially a problem with fusicid acid. The problems with resistance have lead to the recommendation that alternatives to vancomycin be used in combination—such as rifampin with fusicid acid—to treat MRSA (Mulligan, Murray-Leisure, Ribner et al., 1993). While these alternatives to vancomycin exist, they are less than the first choice for treatment of MRSA.

Like penicillin and other antibiotics before it, vancomycin is a starting compound in efforts to produce new and more effective antibiotics.

Semisynthetic Vancomycin

Eli Lilly and Company (1995) has prepared a semisynthetic vancomycin (LY333328) specifically for use against vancomycin-resistant organisms. The drug has demonstrated activity against VRE in animal tests and against MRSA and penicillin-resistant *Strep. pneumoniae* in in vitro tests. According to a company spokesperson, more animal tests of safety and efficacy are required, and, if they are successful, human trials may begin in 1996. This new compound is the product of research centered on development of antibiotics for use against vancomycin-resistant organisms.

Catalytic Antibiotics

Shi and Griffin (1993) discovered that vancomycin has a catalytic (chemical-degrading action) activity, and they are chemically altering vancomycin to develop a molecule that will not only bind to the cell-wall precursor and inhibit cell-wall synthesis, the normal activity of vancomycin, but destroy the precursor as well. If this is achieved, it should increase the potency of vancomycin; the catalytic antibiotic should be able to move to another cell-wall precursor after destroying the first, and so on. Griffin (1994) is also seeking to alter the vancomycin molecule so that it regains its binding affinity to the altered cell-wall precursors that are present in vancomycin-resistant bacteria. Once affinity is restored, the antibiotic can bind to the cell wall precursor, inhibit the synthesis of the wall, and kill the bacteria. If researchers develop the catalytic function so that it destroys the cell-wall precursor, that activity could be added.

The Macrolides

The macrolide antibiotics inhibit protein synthesis. Erythromycin, the most commonly used member of the class, is effective against a broad range of Gram-positive and Gram-negative bacteria, and is available for oral, intravenous, and topical uses. While resistance has been noted in the United States, it is more common in other

[3] Not all vancomycin-resistant enterococcus are resistant to all antibiotics. *Enterococcus faecalis* remains susceptible to ampicillin, as do some strains of *E. faecium.*

countries, and the level of resistance appears related to the level of use (Steigbigel, 1995).

Azithromycin, a closely related molecule, is now being marketed with advertised advantages in being effective against more strains of bacteria than erythromycin, but it is being marketed on the basis of other positive attributes as well. Because it persists in human white blood cells for a few days (rather than a few hours as with some other antibiotics), two tablets of azithromycin on the first day of treatment and one tablet a day for four more days is sufficient for most applications (Pfizer, Inc., 1993). The convenience of this schedule is contrasted with those for other antibiotics that require three or four daily doses for up to 10 days. According to studies referenced in the advertising literature (Pfizer, Inc., 1993), compliance is better, there are fewer side effects, and patient costs are lower. This example illuminates some of the factors, including convenience and cost, as well as effectiveness, that go into marketing of antibiotics.

NEW RESEARCH TOOLS

New techniques in chemistry and molecular biology have immediate application to research and development of antibiotics. Box 5-2 discusses some of those techniques.

ANTIBIOTICS FROM NEW SOURCES

In addition to using new laboratory tools, antibiotic researchers are also exploring new biological sources for antibiotic activities. Unlike the traditional searches that have looked at products from micro-organisms, some current ones are looking at materials from humans and other animals.

Carbohydrates

Carbohydrates called oligosaccharides ["oligo-" a few, "saccharides" sugars] (OS), are ubiquitous on the surface of mammalian cells, and bacteria and viruses adhere to host cell OS as the first step in the process of recognition, adhesion, and infection (Rosenstein et al., 1988). Individual OS are structurally specific for different organisms, and microbial adherence has been referred to as a "lock and key" phenomenon, in which only certain keys (microbial proteins, called "lectins" or "adhesions") "fit" into specific locks (host-cell OS receptors).

Until recently, the complexity of OS structure and the resulting inability to synthesize sufficient OS at reasonable cost hindered OS drug design. The simplest OS—a disaccharide that is composed of only two sugars—can take any of 20 different forms. The problem increases with size; there are 35,560 possible ways to arrange four sugars into tetrasaccharides. In comparison, four amino acids can create only 24 distinct tetrapeptides (Hughes, 1994). These complexities contributed to the formerly high costs that ranged up to $2 million per gram of OS. New techniques have lowered the cost of some OS by 10,000 times to $200 per gram, and OS drug design has accelerated (George, 1994; Glaser, 1994) with applications in treating bacterial diseases, including ulcers.

The bacteria *Helicobacter pylori* causes gastric and duodenal ulcers, and the usual treatment eradicates it and prevents the reappearance of ulcers with a success rate of 70 to above 90 percent. Resistance of *H. pylori* to antibiotics used in the usual therapy is a factor in lower treatment success rates.

Neose Pharmaceuticals (Roth, 1995) has perfected the synthesis of the OS to which *H. pylori* binds, and animal studies have shown that administration of the OS competes with the *H. pylori* binding sites in the digestive tract, causing the *H. pylori* to release from those sites with the bacteria then being eliminated from the body. The OS is identical to an OS found in mothers' milk, and it has extremely low toxicity in animal tests. Phase I clinical trials for toxicity were underway in March 1995.

Up to 80 percent of all hospital-acquired bacterial pneumonias are caused by one of six bacterial species. According to Roth (1995), all six of those bacterial species bind to the same OS, which opens the possibility of treating those infections with a soluble form of the OS. Another

BOX 5-2: Some New Methods for Research in Antibiotics

Structure-Based Drug Design

Traditionally, that is, for 50 or so years, scientists have discovered new antibiotics by screening thousands of natural, synthetic, or semi-synthetic compounds for antimicrobial properties, analyzing the structures of active ones, and modifying active compounds for greater utility. Scientists have discovered many antibiotics serendipitously, usually an expensive and time-consuming process and always an unpredictable one, and many have been discovered and tested in laboratories and in humans long before researchers understood their mechanism of action.

Structure-based drug design (SBDD), on the other hand, begins with an understanding—or physical model—of the drug mechanism, especially the ligand:receptor interaction (Kuntz, 1992). This interaction occurs at the "active site" where the "ligand," in this case the antibiotic, binds to some structure, the "receptor" (or "target") in the bacteria. SBDD employs newer research tools, such as X-ray crystallography, nuclear magnetic resonance spectroscopy, and supercomputer combinatorial chemistry to design new compounds that will bind more tightly to the active site (Knox, 1993; Fan et al., 1994; Balbes et al., 1994; Boyd and Milosevich, 1993).

Targeted Replacement of Segments of Antibiotic Proteins

The bacterium *Bacillus subtilis* produces an antibiotic called surfactin. Stachelhaus, Schneider, and Marahiel (1995) isolated the DNA segments that code for surfactin from *B. subtilis,* and DNA segments from another bacterium, *Bacillis brevis*, and from the fungus, *Penicillium chrysogenum*. Using recombinant DNA techniques, they constructed hybrid *B. subtilis-B. brevis* and hybrid *B. subtilis-P. chrysogenum* DNA molecules that they reinserted into *B. subtilis*. Hybrid DNAs of the first kind coded for recombinant proteins in which some segments of the protein came from *B. subtilis* and some from *B. brevis* hybrids of the second kind resulted in the production of proteins with some segments from *B. subtilis* and others from *P. chrysogenum*.

This experiment demonstrates a method to construct hybrid molecules, and it may have an application to the development of new antibiotics. Because the DNA segments can come from unrelated organisms, or even from chemical synthesis, the structure of the recombinant DNA, and the resulting protein, can be specified. Better understanding of ligand:receptor interactions may provide the information for the construction of recombinant DNA molecules that will code for new antibiotics.

"Unnatural" natural products

The bacterium *Streptomyces coelicolor* produces the antibiotics tetracyclines and erythomycin, which are members of a class of compounds called polyketides. Scientists have discovered more than 10,000 polyketides, including many useful drugs, but the percentage of medically useful compounds in the total number of discovered natural polyketides has decreased in recent years (Lipkin, 1995). McDaniel et al., (1995) have categorized the enzymes involved in the synthesis of polyketides and constructed plasmids that contain genes for those enzymes. When expressed in *S. coelicolor,* the genes on the plasmids resulted in the synthesis of new polyketides.

Based on their understanding of the activities of the enzymes, McDaniel et al., (1995) devised rules for the bioengineered synthesis of polyketides, and they suggested that chemists will be able to generate bioengineered (unnatural) products that will be as diverse as the thousands of polyketides already seen in nature. The expectation is that medically useful compounds will be generated.

(continued)

BOX 5-2: Some New Methods for Research in Antibiotics (Cont'd.)

In vivo Expression Technology

Traditional research has sought microbial virulence factors by culturing and growing microbes in the laboratory and then examining the products of bacterial growth that are present in the culture broth. Well-known examples of such products are diphtheria and cholera toxins which were used for vaccine development.

Mekalanos and his colleagues (Mahan, Slauch, and Mekalanos, 1993) acted on the idea that bacteria are "Trojan Horses," hiding their virulence factors and toxins until specific host signals cause them to be released. Such genes would cause the production of proteins that could be the targets for antibiotics or antigens for the production of vaccines. Mahan et al., (1993) call the technology to explore such hidden bacterial strategies "in vivo expression technology" (IVET), which has been heralded as "revolutionary" (Barinaga, 1993).

IVET may be applied to the problem of antibiotic resistance in at least two ways. First, it can identify new antimicrobial targets. Nearly half of the Salmonella genes detected with IVET were previously unknown. The products of these genes are potential targets for new antibiotic design. Second, IVET may guide production of new vaccines, as previously unknown products of IVET-identified genes give vaccine developers new immunogens against which humans can be inoculated.

Antibiotics Targeted Against a Bacterial Regulatory System

In bacteria, some RNA synthesis depends on a two-step regulatory system. The first component is a sensor protein in the bacterial membrane that can detect a signal in the environment, say, a sugar or other nutrient of use to the bacterium. In response, the sensor chemically adds a phosphate to itself and to another protein, the transducer. The phosphorylated transducer then activates RNA synthesis from specific sites on the DNA, and the RNA is used to direct synthesis of enzymes necessary to transport the nutrient into the bacterial cell, for its metabolism, or for some other aspect of biochemistry associated with the nutrient.

Virulence genes, as detected by IVET or other methods, are probably regulated by a two-component system, with the sensor detecting some chemical in the host animal or host cell. A substance that interferes with the regulatory system might be a useful antibiotic, and such substances have been described. The two-component regulatory system does not exist in mammalian cells, making toxic side effects from such antibiotics unlikely (Salyers and Whitt, 1994).

OS designed to lower the risk of infant infections is modeled after naturally occurring OS found in mothers' milk (Neose Pharmaceuticals, 1994).

Microbial resistance to OS is predicted to be small because two independent genetic events would have to take place. First, the bacterium would have to mutate so that it would no longer bind to the OS; that would also make it non-infective because it could not bind to OS on cell surfaces. Only a second mutation that produced a mechanism to bind to another molecule on the surface of the stomach cell could restore bacterial infectivity.

Antibiotic Peptides

Among the most widely studied of the "new" antibiotics are peptide antibiotics. Within this large group of molecules are bactericidal/permeability increasing proteins (BPI), magainins, and cecropins.[4] Their common antimicrobial activity

[4] These agents are included here to be illustrative; this list is not inclusive. J.E. Gabay provides a short description of these and some other antimicrobial peptides as well as a useful reference list in "Vbigitous and natural antibiotics," *Science* 264:373–374, 1994.

results from increasing bacterial permeability, and in this regard they are similar to the topical peptide antibiotic polymyxin B, produced by the bacterium *Bacillus polymyxa*. Scientists, however, know few specifics about their mechanisms of action (Gabay, 1994). New technologies that allow researchers to synthesize and screen "combinatorial libraries" consisting of tens of millions of natural and synthetic peptides (Blondelle et al., 1994) have increased the capacity to make and test candidate peptide antibiotics.

Bactericidal/Permeability Increasing Peptide

Weiss et al. (1978) reported isolation of a bactericidal protein from human and rabbit cells that appeared to cause an "almost immediate" breakdown of the bacterial permeability barrier to the entry of the antibiotic actinomycin D. While BPI was bactericidal to several strains of *E. coli* and *Salmonella typhimurium*, both Gram-negatives, it had no effect on Gram-positive bacteria or the yeast Candida.

Using molecular biology techniques, scientists produced a fragment of the BPI molecule (called rBPI-23) that increased bactericidal activity, including activity against penicillin-resistant strains of *Streptococcus pneumoniae* (Lambert, 1994), and enhanced the efficacy of co-administered antibiotics (Meszaros et al., 1994). Human subject testing has recently begun with another fragment (rBPI-23). When administered along with low doses of endotoxin, a toxin produced by Gram-negative bacteria, rBPI-23 blunted the adverse effects of the endotoxin, was well tolerated by the volunteers, and was not immunogenic (von der Mohlen, 1994).

Magainins

Science, like all human pursuits, has its own folklore, and the discovery of the magainins passed immediately into the legends of science. In the late 1970s, a researcher at the National Institutes of Health was studying RNA expression in the African clawed frog, *Xenopus laevis*. He noted that the frogs never developed postoperative inflammation or wound infections–even though surgical procedures were performed under non-sterile conditions–and he wondered if "there might be a 'sterilizing' activity in the skin." Zasloff (1987) isolated two closely related peptides with broad-spectrum bactericidal activity that were also active against some single-celled parasite species. He named the two peptides "magainin 1" and "magainin 2" (Hebrew for "shield").

The magainins are short peptides that insert into the bacterial cell membrane and open up channels that lead to the death of the bacteria. Thousands of magainin analogues have been synthesized with the goal of increasing antimicrobial activity (Cuervo et al., 1988). One magainin, MSI-78, is now in phase III trials, which are expected to be completed in mid-1996. If that schedule is kept, Magainin Pharmaceuticals expects to file an NDA at the end of that year for the sale of MSI-78 as a topical antibiotic (Magainin Pharmaceuticals, 1994); however, an earlier trial of this magainin against impetigo was suspended because of disappointing results. Other magainins are undergoing toxicity tests in animals in expectation that they will find application as systemic antibiotics.

Cecropins

Cecropins are peptides from the North American silk moth, *Hyalophora cecropia*. They are similar in size to the magainins, and like the magainins, they increase bacterial permeability. Researchers have chemically combined cecropin with another natural peptide antibiotic, mellitin, derived from bee venom. The resulting product demonstrated activity against *S. aureus* and *Plasmodium falciparum* (Blondelle and Houghten, 1992). More recently, a recombinant cecropin/mellitin hybrid was shown to be bactericidal against *Pseudomonas aeruginosa*. Other antimicrobial cecropins and cecropin-like molecules have been recently isolated from the hemolymph of the silk worm *Bombyx mori*, the male reproductive tract of the fruitfly *Drosophila melanogaster*, and from the intestines of pigs.

Defensins

Defensins are broad-spectrum antimicrobial peptides isolated from mammalian cells, including epithelial cells lining the human small intestine (Blondelle and Houghten, 1992). Although similar in size to magainins and cecropins, defensins differ in chemical structure. The isolation of a related group of molecules isolated from cow airways, called "ß-defensins," has added to the theory that defensins form a natural, primary mucosal defense against microbial pathogens and are therefore potentially powerful new antimicrobial agents (Taylor, 1993).

Lactoferrin, a Substance with Antibiotic Properties from Human Milk

Lactoferrin, the second most abundant protein in human milk, is bacteriostatic *in vitro* and in tissue culture tests against a variety of bacteria, including MRSA. Three different mechanisms contribute to the bacteriostatic activity of lactoferrin: It binds iron, thereby depriving bacteria of that essential element, it increases bacterial permeability, and it activates immunological defenses. Ward et al., (1995) recently described a method to produce human lactoferrin in the laboratory, and the product has the same antibiotic properties as the human protein. Pre-clinical studies are now under way with the laboratory-produced chemical (Ward et al., 1995; Wyatt, 1995).

Human milk has antibacterial properties, and some of those properties reside in lactoferrin. Lactoferrin is also found in other external secretions—tears, nasal secretions, saliva, and genital secretions—all of which have antibacterial properties. Those secretions have been around for millions of years and they are still effective against bacteria. Development of lactoferrin, or other substances with antibiotic activity from humans, as antibiotics might provide therapies that will not elicit resistance.

Like all the protein antibiotics, lactoferrin presents administration difficulties because they cannot be absorbed from the digestive tract, thereby eliminating oral uses. They can be used topically, as polymyxin B, and they may find use against enteric infections and pulmonary infections, where they might be administered by aspiration.

Steroid Antibiotics

The discoverer of magainins also wondered over the rarity of infections in fetal dogfish sharks (*Squalus acanthis*), despite the fact that mother sharks flush their fallopian tubes regularly with seawater to remove fetal wastes. Moreover, he noted that the sharks rarely became infected after surgery. Using the same methodology as the one used for magainins, he and co-workers successfully isolated squalamine from shark stomach, liver, gall bladder, spleen, testes, gills, and intestine. Squalamine is a steroid compound, closely-related to cholesterol (Moore et al., 1993) and has antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as fungi and protozoa. Testing of squalamine is now at the pre-clinical stage.

"Anti-Sense" Nucleotides

One of the more frequently proclaimed "magic bullets" against drug-resistant bacteria is "anti-sense" molecules (Stein and Cheng, 1993) that bind to critical DNA or RNA segments in the bacterial cell and disrupt their functioning. A variety of new technologies, many developed for application in the federally funded Human Genome Project, allow for simpler and more rapid DNA sequencing and have made investigations of anti-sense therapy feasible.

Like many new therapies, the oligionucleotides (ON), the segments of DNA and RNA molecules that would be used as anti-sense molecules, present many challenging problems. New technologies need to be developed for the bulk synthesis of ON and to transport ON through the body and inside bacterial cells, and methods may have to be developed to deliver the ONs to their complementary DNA or RNA target (Rahman et al., 1991). "Oligonucleotide-like" molecules will be required to circumvent the instability and rapid degradation of ON in the body, and some

such molecules have been synthesized and shown to have improved stability.

GETTING NEW ANTIBIOTICS TO MARKET

This chapter reviews some ideas for new antibiotics, and any of those ideas will require significant investments to support the research and development necessary to bring it through clinical trials and to market. In 1993, OTA (1993) comprehensively reviewed the return on investments in pharmaceutical research and development. This section contains a brief review of some of the issues related to pharmaceutical developments specifically focused on antibiotics.

Antibiotics are used for short periods of time, and representatives of some pharmaceutical companies claim that greater profit is to be made in developing drugs for chronic illnesses such as heart disease and arthritis, for which drugs may be necessary every day for years at a time. The counter-argument to that contention is that a life-saving drug with no alternative, even if used only rarely, can command a high price. Resistance limits the market life of antibiotics: As they lose some of their efficacy, they become less profitable. At the same time, antibiotic resistance opens up new markets.

Participants at OTA advisory panel meetings said that major pharmaceutical companies are not likely to mount a research and development effort for potential annual markets of less than $100 million. They also stated that some smaller companies, generally lumped under the rubric of "biotech firms," could do very well on a market of $20 to $30 million a year.

Some antibiotics, however, have generated major markets. As shown in box 5-3, a single antibiotic can account for 15 percent of a major manufacturer's sales. Such a percentage is probably unusual, but it indicates that an antibiotic can be a major source of revenue.

A new antibiotic that overcomes resistance has a ready market. There are approximately 19,000 VRE cases yearly. If an antibiotic effective against VRE were developed, OTA assumes the company that marketed it could charge a high price because no other antibiotic is available for that use, but OTA did not try to estimate that price. There are about 60,000 MRSA cases annually, and some proportion of those are treatable only with vancomycin. For illustrative purposes, OTA assumes that all 60,000 cases are now treated with vancomycin, that the antibiotic costs $100 per day, and that the treatment requires 10 days. That market is then $60 million annually (60,000 cases per year $\times$ $100 per day $\times$ 10 days of treatment per case), and the new antibiotic would be competing for that market with vancomycin.

A major company might not be interested in this market; it is well below $100 million per year. But the new antibiotic could probably be used for many other infections, and the market could be much larger, with, most likely, earlier emergence and spread of resistance than if the antibiotic were restricted to use against MRSA.

Whatever the size of market for an antibiotic, it is expected to erode with the development of antibiotic-resistant bacteria. Control of the emergence and spread of resistance would result in a longer market life and greater sales and profits. However, the major way known to slow down resistance is to minimize the use of the antibiotic, which would have an adverse effect on sales and profits, at least in the short run. To return to the hypothetical example of an antibiotic to treat MRSA, restricting the use of the drug would prolong its effectiveness before resistance developed. That restriction would also reduce sales compared to those expected if there were unrestricted use against all respiratory infections, for example. This tradeoff is discussed further in the following section.

BOX 5-3: Patent Protection and Post-Patent Hurdles for Competitors (News media clips)

"Generic Erosion for Ceclor?

"When Lilly's Ceclor (cefaclor) comes off patent in the U.S. in 1992, unit sales of the antibiotic, which account for roughly 15 percent of the company's total sales, could be eroded by 70 to 80 percent by generic competition in the first 18 months, according to Kidder, Peabody analyst James Flynn.

"This erosion will take place despite the fact that Lilly holds process patents for Ceclor which expire between 1994 and 2006, and plans to introduce a sustained-release formulation, Ceclor AF, the analyst predicts.

"Recent legal action in Japan, where Lilly has filed suit against 10 companies for alleged infringement of its cefaclor patent, suggest that the company intends to defend its patents vigorously.... However, Mr. Flynn argues that Lilly's process patents will not be recognized in a number of countries (e.g., Italy) which are likely to be used as manufacturing sites for generic companies planning to import formulations of cefaclor on expiration of the product patent.

"Barr and Biocraft, which have valid cephalosporin manufacturing facilities in the U.S., may also try to 'skirt' Lilly's process patents, Mr. Flynn says. Such a strategy would give these companies a 'meaningful cost advantage' over importing firms, he adds.

"Ceclor AF is unlikely to be introduced in the United States much before the cefaclor product patent expires, Mr. Flynn says. A preferred dosing regimen is the only benefit he is aware Ceclor AF would have over generic competition. The analyst notes that Lilly's keftabs formulation of Keflex (cefalexin) gained less than 15 percent of Keflex' sales after the 1987 product patent expired."

SOURCE: "Generic Erosion for Ceclor," *Scrip World Pharmaceutical News* 1594:25, 1991.

"Ceclor Market Dominance Will Continue Past Dec. 1992 Patent Expiration, Lilly Contends: Process Protection Thru 1994

"Lilly's dominant position in the oral antibiotic market will survive the expiration of the U.S. patent on Ceclor in December 1992, the company maintained at a meeting with financial analysts in New York on Feb. 28. Based on a process protection for cefaclor and a pending NDA application for the follow-up compound loracarbef, Lilly is forcefully declaring its intention to hold its place in the oral antibiotic field....

"Asked to comment on the impact of the upcoming patent expiration on Ceclor sales, Lilly Pharmaceutical President Gene Step said the relevant questions should be what will be Lilly's overall position in the oral antibiotic market and what is the likelihood of generic versions of cefaclor reaching the market.

"'You really have to [ask] what is our participation in the oral antibiotic market and to what extent will that be affected' by generic cefaclor or 'by other products that we may or may not be selling' in the future, Step said.

"Lilly is emphasizing the *de facto* protection of a difficult production process and a patent position on a late-stage intermediate... Step declared that when all factors are considered Ceclor should 'remain a viable product for Eli Lilly beyond expiration of the patent.'

"As the company often has been pointing out recently, Step told the Feb. 28 meeting that Ceclor has yet to face generic competition outside the U.S., even in markets where there is no patent protection. 'While we cannot know what the actions of everybody else in the world will be,' Step said, 'it is very interesting to observe that while there isn't patent coverage in a large part of the world for Ceclor, there isn't any generic Ceclor.'

(continued)

BOX 5-3: Patent Protection and Post-Patent Hurdles for Competitors
(News media clips) (Cont'd.)

"Lilly Research Labs President Mel Perelman explained the process protection during question-and-answer. 'The Ceclor synthetic route is so long and so complex' that it will be difficult to duplicate, Perelman said....

"A producer of cefaclor can take a number of different routes to get to the intermediate, Perelman explained, 'but they can't go through it without violating our patent. So an ethical or legal end-run seems extremely improbable.' The patent on the intermediate runs until December 1994. Step further pointed out that establishing a cefaclor manufacturing process 'will require very considerable capital investment...we haven't seen that yet'...."

SOURCE: Ceclor market: Quoted from "Ceclor Market Dominance Will Continue Past Dec. 1992 Patent Expiration, Lilly Contends: Process Protection Thru 1994, Lorabid NDA Filed as Backup," FDC Reports: Prescription and OTC Pharmaceuticals, March 4, 1991. p. 15.

"Ivax Corp. faces lawsuit from Eli Lilly"

In 1995, Eli Lilly sued Ivax Corporation, a pharmaceutical company that announced that it had received FDA approval to manufacture cefaclor capsules, a generic version of Lilly's Ceclor. Lilly claimed that Ivax's supplier of a raw material used a process that infringes on Lilly's process patents.

SOURCE: Ft. Lauderdale, FL *Sun-Sentinel.* 1995. April 29, 1995. p. 8B.

PATENTS

Patents provide the primary protection for a pharmaceutical company's investment in research, development, marketing, and production costs. The 1991 OTA report, *Biotechnology in a Global Economy,* described the patent process for pharmaceuticals:

> Drug companies usually secure patent protection early in drug development, before the drug enters the regulatory process. Regulatory approval for new drugs takes, on average, 7 to 10 years to complete. This translates into a 7- to 10-year reduction in [the usual 17-year] patent protection for pharmaceutical products when they reach the market, leaving such products with, on average, 9 years of protected life.....
>
> [T]he Drug Price Competition and Patent Term Restoration Act of 1984... restores part of the patent life lost due to lengthy regulatory approval. The act allows extension of the patent term for up to 5 years, but it does not allow extension beyond 14 years for effective patent life. The actual extension granted is equal to the total time taken by the Food and Drug Administration (FDA) to review the New Drug Application, plus one-half of the clinical testing time. In addition, the act promotes generic competition by providing FDA with an Abbreviated New Drug Application (ANDA) process. This process facilitates the approval of generic drugs by eliminating the need for costly clinical studies. An ANDA does require the sponsoring company to demonstrate its generic's bioequivalence to the pioneer drug. This is much less costly and time-consuming than complete clinical trials and facilitates the market entrance of generic drugs.

The GATT (General Agreement on Tariffs and Trade) legislation changed patent terms from 17 years from issuance to 20 years from filing (OTA, 1991, discusses the nuances of these terms), and in March 1995, the U.S. Patent and Trademark Office (PTO) announced a preliminary policy statement that extensions would be added to the new 20-year patent term. In June 1995, however, PTO reversed its position and presented manufacturers a choice between adding any extension they had to the 17-year term or accepting the 20-year term under GATT. Manufacturers are expected to challenge this decision in court.

Members of the OTA advisory panel discussed the pluses and minuses of a negotiated agreement between a manufacturer and the PTO to extend the patent life of an antibiotic in exchange for restrictions on its use. Again, consider the example of an antibiotic effective against MRSA. Could PTO, FDA, and the manufacturer work out an agreement so that the antibiotic was marketed only for use against MRSA? Such an agreement would have a positive impact on the emergence of resistance, but it would present supervision or enforcement problems to assure that the restrictions were followed. It would also present problems for the manufacturer in estimating its returns from unrestricted sales over a few years—until resistance becomes common—as compared to restricted sales over more years. How soon resistance would arise in both cases is difficult to estimate, as are the chances of another company developing a comparable or better drug.

Many compounds are patented but never brought to market. If, subsequently, it was discovered that such a compound was useful against antibiotic-resistant bacteria, probably no firm would be interested in conducting the tests and trials necessary to bring it to market. Without patent protection, the firm that paid for the tests and trials would be unable to recover its costs. Fusidic acid, an antibiotic that has been used in Denmark and other countries since 1962 (Mandell and Sande, 1995), provides a real-life example of such a drug. Fusidic acid is active against at least some strains of MRSA, and it is used against those bacteria in other countries. It has never been marketed in the United States, although it can be made available under compassionate use procedures to physicians in this country. Because it is off-patent, the company that developed and sells it elsewhere is not willing to fund clinical trials that would be necessary to obtain FDA approval for its being marketed for use against MRSA here.

Patent protection of the chemical substance is not the only method by which companies can maintain their markets. OTA (1993, p. 82-87) describes how complicated and expensive production methods and facilities can be a major hurdle for competitors, especially when the methods and facilities are protected with process patents. For example, in 1995, Ivax Corporation announced it had received FDA approval to manufacture a generic version of a cephalosporin on which the patent had expired in 1992. Eli Lilly sued Ivax, claiming that Ivax's supplier of a raw material used a process that infringed upon Lilly's process patents (Fort Lauderdale *Sun-Sentinel*, 1995).

PRICING OF DRUGS DEVELOPED IN PART BY FEDERAL RESEARCH

The Federal Technology Transfer Act of 1986 (P.L. 99-502) authorized the establishment of CRADAs (Cooperative Research and Development Agreements) between federal intramural laboratories and private industry to bring inventions and discoveries in federal laboratories to market. In exchange, the private industries would receive the profit from sales of the developed products. In 1989, Congress directed the National Institutes of Health (NIH) to require "reasonable pricing" of any drugs that were developed in cooperation between its laboratories and industry. Industry objected to the restrictions on pricing, and, in April 1995, NIH relinquished its right to require reasonable pricing.

This change is expected to have little affect on antibiotics. While the federal government conducts research on antiviral and antifungal agents, it has supported little research on antibacterials, leaving that research to the pharmaceutical firms, and none of the six products that had been developed as of April 1995 through CRADAs was a drug (*Health News Daily*, 1995).

CONCLUSIONS

Antibiotic research and development, as almost all drug research and development in the United States, is carried out and sponsored by pharmaceutical companies. Recent years have seen the introduction of few new antibiotics into the mar-

ket, which may reflect a diminished research effort in antibiotics five, 10, and more years ago.

Currently, there is a great deal of activity in looking for substances with antibiotic properties in biological sources that have not been exploited in the past and in applying new molecular biologic and chemical techniques to the synthesis of antibiotics and to understanding their mechanisms of action. On the positive side, some of the compounds being considered as possible antibiotics have mechanisms of action different from those of currently used antibiotics, and they should be especially useful against bacteria now resistant to many or all currently available antibiotics. Despite that promise, there is great uncertainty about if and when there will be a pay-off from the research efforts, and few experts expect commercial availability of any antibiotics with new mechanisms of activity in this century. The uncertainty about availability of new antibiotics underlines the importance of efforts to reduce the emergence and spread of bacteria resistant to now-used antibiotics.

The emergence of antibiotic-resistant bacteria produces new market opportunities, and it can be expected that pharmaceutical firms will be interested in developing products for it. Some experts argue, however, that the profits to be expected from an antibiotic are smaller than those from other drugs and that pharmaceutical firms will focus their efforts on other, more profitable drugs. On the other side of that argument, an antibiotic that is effective against an infection resistant to all other antibiotics could probably be sold at a very high price.

REFERENCES

Balbes, L.M., S.W. Mascarella, and D.B. Boyd. 1994. A perspective of modern methods in computer-aided drug design. *Comprehensive Reviews Chemistry 5*:337-379.

Barinaga, M. 1993. New technique offers a windown on bacteria's secret weapons. *Science 259*:595.

Bergeron, J., L. Wondrack, M. Ammirate, *et al*. 1994. Glycycyclines evade both ribosomal and efflux tetracycline resistance mechanisms. Presented at First International Conference on Antibiotic Resistance: Impact on Discovery. Englewood, CO. Sept. 1994.

Blondelle, S.E., and R.A. Houghten. 1992. Progress in antimicrobial peptides. *Annual Reports in Medicinal Chemistry 27*:159-168.

Blondelle, S.E., E. Takahashi, P.A. Weber, *et al*. 1994. Identification of antimicrobial peptides by using combinatorial libraries made up of unnatural amino acids. *Antimicrobial Agents and Chemotherapy 38*:2280-2286.

Boyd, D.B. and S.A.F. Milosevich. 1993. Supercomputing and drug discovery research. *Perspectives Drug Discovery and Design 1*:345-348.

Bristol-Meyers Squibb. 1995. The "Hand-Offs" at Bristol-Myers Squibb. Biotechnology Industry Advertising Supplement. *Science 267*:1692.

Bushby, S.R.M., and G. H. Hitchings. 1968. Trimethoprim, a sulfonamide potentiator. *British Journal of Pharmacology and Chemotherapy 33*:72-90.

Buttle, G.A.H., W.E. Gray, and D. Stephenson. 1936. Protection of mice against streptococcal and other infections by p-aminobenzenesulphonamide and related substances. *Lancet i*:1286-1290.

Colebrook, L., and M. Kenny. 1936. Treatment of human puerperal infections, and of experimental infections in mice with prontosil. *Lancet i*:1279-1286.

Cuervo, J.H, B. Rodriguez, and R.A. Houghten. 1988. The magainins: sequence factors relevant to increased antimicrobial activity and decreased hemolytic activity. *Peptide Research 1*:81-86.

Eli Lilly and Company. 1995. Lilly announces development of a compound to address antibiotic resistance. Press release, March 28.

Emori, T.G. and R.Y. Gaynes. 1993. An overview of nosocomial infections, including the role of the microbiology laboratory. *Clinical Microbiology Reviews 6*:428-442.

Fan, C., P.C. Moews, C.T. Walsh, *et al*. 1994. Vancomycin resistance: Structure

of D-alanine:D-alanine ligase at 2.3 angstrom resolution. *Science 266*:439-443.

Fekety, R. 1995. Vancomycin and teicoplanin. In: G.L. Mandell, J.E. Bennett, and R. Dolin (eds.) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. Churchill Livingstone: New York, NY. pp 346-354.

Fort Lauderdale (FL) *Sun-Sentinel*. 1995. Ivax Corp. faces lawsuit from Eli Lilly. April 29. p. 8B.

Frankel, D.H. 1995. Designing New Antibiotics. Contractor report to the Office of Technology Assessment. Photocopied typescript. January.

Frieden, T.R. and R.J. Mangi, 1990. Inappropriate use of oral ciprofloxacin. *Journal American Medical Association 264*:1438-1440.

Gabay, J.E. 1994. Ubiquitous natural antibiotics. *Science 264*:373-374.

George, J. 1994. Biopharmaceutical company raises $10M. *Philadelphia Business Journal 13*:1,27.

Georgopapdakau, N.H., A. Bertasso, K.K. Chan, *et al*. 1989. Mode of action of the dual-action cephalosporin Ro-23–9424. *Antimicrobial Agents and Chemotherapy 33*:1067-1071.

Georgopapdakau, N.H., and A. Bertasso. 1993. Mechanisms of action of cephalosporin 3'-quinolone esters, carbamates, and tertiary amines in Escherichia coli. *Antimicrobial Agents and Chemotherapy 37*:559-565.

Glaser, V. 1994. Carbohydrate biotechnology enters the domain of rational drug design. *Genetic Engineering News*, July, p. 6,7,11.

Gootz, T.D. 1990. Discovery and development of new antimicrobial agents. *Clinical Microbiology Reviews 3*:13-32.

Griffin, J.H. 1994. Research summary. Department of Chemistry, Stanford University, Palo Alto, CA (data on file).

Health News Daily. 1995. NIH removes "reasonable price" clause from standard CRADA agreement. April 12, p. 2-3.

Hooper, D.C. and J.S. Wolfson. 1989. Bacterial resistance to the quinolone antimicrobial agents. *American Journal Medicine 87 (suppl 6C)*:17S-23S.

Hughes, S. 1994. Carbohydrate research—a new source of therapeutics. *Scriptorium* Apr., pp. 28-31.

Husain, R.A. 1991. Disturbing susceptibility pattern for ciprofloxacin. *American Journal Public Health 48*:1892.

Journal of Antimicrobial Chemotherapy. 1992. RP 59500: a semi-synthetic injectable streptogramin antibiotic. Supplement A to Volume 30, July.

Knox, J.R. 1993. Crystallography of penicillin-binding enzymes. In: Bentley, P.H. and R. Ponsford (eds.) *Recent Advances in the Chemistry of Anti-infective Agents*. Royal Society of Chemistry: Cambridge, England. pp. 37-49.

Kuntz, I.D. 1992. Structure-based strategies for drug design and discovery. *Science 257*:1078-1082.

Lambert, L. 1994. rBPI-21 kills both gram-positive and gram-negative bacteria. Paper presented at 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL. Oct. 4-7.

Levy, S.B. 1981. The tetracyclines: microbial sensitivity and resistance. In: G.G. Grassi, and L.D. Sabath (eds.) *New Trends in Antibiotics: Research and Therapy*. Elsevier/ North Holland Biomedical Press: New York, NY. pp. 27-44.

Levy, S.B. 1992. *The Antibiotic Paradox*. Plenum Press: New York.

Lipkin, R. 1995. New "design rules" yield novel drugs. *New Scientist 147*:374.

Magainin Pharmaceuticals, Inc. Plymouth Meeting, PA. 1994. (data on file).

Mahan, M.J., J.M. Slauch, J.J. Mekalanos. 1993. Selection of bacterial virulence genes that are specifically induced in host tissues. *Science 259*:686-688.

Mandell, G.L., and M.A. Sande. 1990. Antimicrobial agents (continued). In: A.G. Gilman, T.W. Rall, A.S. Nies, et al. (eds.) *The Pharmacological Basis of Therapeutics*. Pergamon Press: New York, NY. pp.1047-1065.

McDaniel, R., S. Ebert-Khosla, D.A. Hopwood, and C. Khosla. 1995. Rational design of aromatic polyketide natural products by recombinant assembly of enzymatic subunits. *Nature 375*:549-554.

Meszaros, K., S. Aberle, K. Lin, and J.B. Parent. 1994. Recombinant fragment of bactericidal/permeability increasing protein (rBPI-21) and complement activation by Lipid A and rough bacteria. Paper presented at 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL. Oct. 4-7.

Modern Healthcare. 1994. Restraint on use of antibiotics urged. June 13, p. 47.

Moore, K.S., S. Wehrlii, H. Roder, *et al*. 1993. Squalamine: an aminosterol antibiotic from the shark. *Proceeding of the National Academy of Science 90*:1354-1358.

Mulligan, M.E., K.A. Murray-Leisure, B.S. Ribner, *et al*. 1993. Methicillin-resistant *Staphylococcus aureus*: A consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. *American Journal Medicine 94*:313-328.

Nelson, M.L., B.H. Park, J.S. Andrews, *et al*., 1993. Inhibition of the tetracycline efflux antiport protein by 13-thio-substituted 5-hydroxy-6-deoxtetracyclines. *Journal of Medicinal Chemistry 36*:370-377.

Nelson, M.L., B.H. Park, and S.B. Levy. 1994. Molecular requirements for the inhibition of the tetracycline antiport protein and the effect of potent inhibitors on the growth of tetracycline-resistant bacteria. *Journal Medicinal Chemistry 37*:1355-1361.

Neose Pharmaceuticals, Inc. Horsham, PA. 1994. (data on file).

Nikaido, H. 1994. Prevention of drug access to bacterial targets: permeability barriers and active efflux. *Science 264*:382-388.

Pfizer, Inc. 1993. Advertising folder for azithromycin antibiotic. Pfizer U.S. Pharmaceutials Group, New York, NY.

Rahman, M.A., J. Summerton, E. Foster, *et al*. 1991. Antibacterial activity and inhibition of protein synthesis in *Escherichia coli* by antisense DNA analogs. *Antisense Research and Development 1*:319-327.

Reading, C., and M. Cole. 1977. Clavulanic acid: a ß-lactamase inhibiting ß-lactam from *Streptomyces clavuligerus*. *Antimicrobial Agents and Chemotherapy 11*:852-857.

Rhone-Poulenc Rorer. 1995. *1994 Summary Report: Building for the Future*. Report to stockholders. Rhone-Poulenc Rorer, Collegeville, PA.

Rosenstein, I.J., T. Mizouchi, E.F. Hounsell, *et al*. 1988. New type of adhesive specificity revealed by oligosaccharide probes in *Escherichia coli* from patients with urinary tract infections. *Lancet ii*:1327-1330.

Roth, S. 1995. Neose Pharmaceutical, Horsham, PA. Personal communication.

Roth, S., and D. Zopf. 1994. Oligosaccharide pharmaceuticals. In: D.B. Weiner, and W.V. Williams (eds.) *Biological Approaches to Rational Drug Design*. CRC Press: Boca Raton, FL. p. 137-147.

Salyers, A.A. and D.D. Whitt. 1994. *Bacterial Pathogenesis*. ASM Press: Washington, DC. p. 63-72.

Schaechter, M., G. Medoff, and B.I. Eisenstein (eds). 1993. *Mechanisms of Microbial Disease (Second Editon)*. Williams and Wilkins: Baltimore, MD.

Shi, Z., and J.D. Griffin. 1993. Catalysis of carbamate hydrolysis by vancomycin and semisynthetic derivatives. *Journal of the American Chemical Society 115*:6482-6486.

Stachelhaus, T., A. Schneider, and M.A. Marahiel. 1995. Rational design of peptide antibiotics by targeted replacement of bacterial and fungal domains. *Science 269*:69-72.

Steigbigel, N.H. 1995. Macrolides and clindamycin. In: G.L. Mandell, J.E. Bennett, and R. Dolin (eds.) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. Churchill Livingstone: New York, NY. p. 334-346.

Stein, C.A., and Y.C. Cheng, Y-C. 1993. Antisense oligonucleotides as therapeutic agents–is the bullet really magic? *Science 261*:1004-1011.

Sum, P-E., V.J. Lee, P.T. Petersen, *et al*. 1994. Novel glycylcycline derivatives: the design, synthesis and structure-activity relationship of 7-(substituted)-9(substituted glycylamid)-6dimethyl-6 deoxytetracyclines. Paper presented at 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, Fl., October 4-7.

Sum, P.E., V.J. Lee, and F.P. Tally. 1994. Synthesis of novel tetracycline derivatives with substitution at the C-8 position. *Tetrahedron Letters 35*:1835-1836.

Taylor, R. 1993. Drugs "R" us: finding new antibiotics at the endogenous pharmacy. *Journal of NIH Research 5*:59-63.

U.S. Congress, Office of Technology Assessment. 1991. *Biotechnology in a Global Economy*. (OTA-H-494). U.S. Government Printing Office: Washington, DC.

U.S. Congress, OTA (Office of Technology Assessment). 1993. *Pharmaceutical R&D: Costs, Risks and Rewards*. (OTA-H-522). U.S. Government Printing Office: Washington, DC.

U.S. Department of Health and Human Services, Food and Drug Administration. 1995. Comments to OTA on earlier draft of this report. June 16.

von der Mohlen, M. 1994. Effects of rBPI-23 on endotoxin-induced cytokine release and leukocyte changes in human volunteers. Presented at 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL, Oct. 4-7.

Ward, P.P., C.S. Piddington, G.A. Cunningham, *et al*. 1995. A system for production of commercial quantities of human lactoferrin: A broad spectrum natural antibiotic. *Bio/Technology 13*:498-503.

Wyatt, R.D., Agennix Inc., Houston, TX. 1995. Personal communication. July 13.

Weiss, J., P. Elsbach, I. Olsson, *et al*. 1978. Purification and characterization of a potent bactericidal and membrane active protein from the granules of human polymorphonuclear leukocytes. *Journal of Biological Chemistry 253*:2664-2672.

Zasloff, M. 1987. Magainins, a class of antimicrobial peptides from *Xenopus* skin: isolation, characterization of two active forms, and partial cDNA sequence of a precursor. *Proceeding of the National Academy of Science 84*:5449-5453.

New Technologies for Infection Diagnosis and Control

6

Three major options exist for the control of bacterial diseases: 1) disrupt or halt transfer of bacteria from person to person and from the environment to people, 2) treat cases of disease with antibiotics, and 3) prevent disease through vaccination. This chapter describes diagnostic methods that guide the selection and use of antibiotics, the use of vaccines, methods for delivery of high concentrations of antibiotics to areas of localized infections, devices and materials designed to reduce the transfer of bacteria in the hospital, and some treatment methods used before the antibiotic age.

The cartoon, which is adapted from one that originally appeared in *Science*, is a humorous look at the serious problem posed by bacteria resistant to all available antibiotics. Some bacteria are expected to develop resistance to any antibiotic introduced into medical practice. Therefore, continued improvement in infection diagnosis and control is necessary to optimize the use of antibiotics and slow the spread of resistant bacteria.

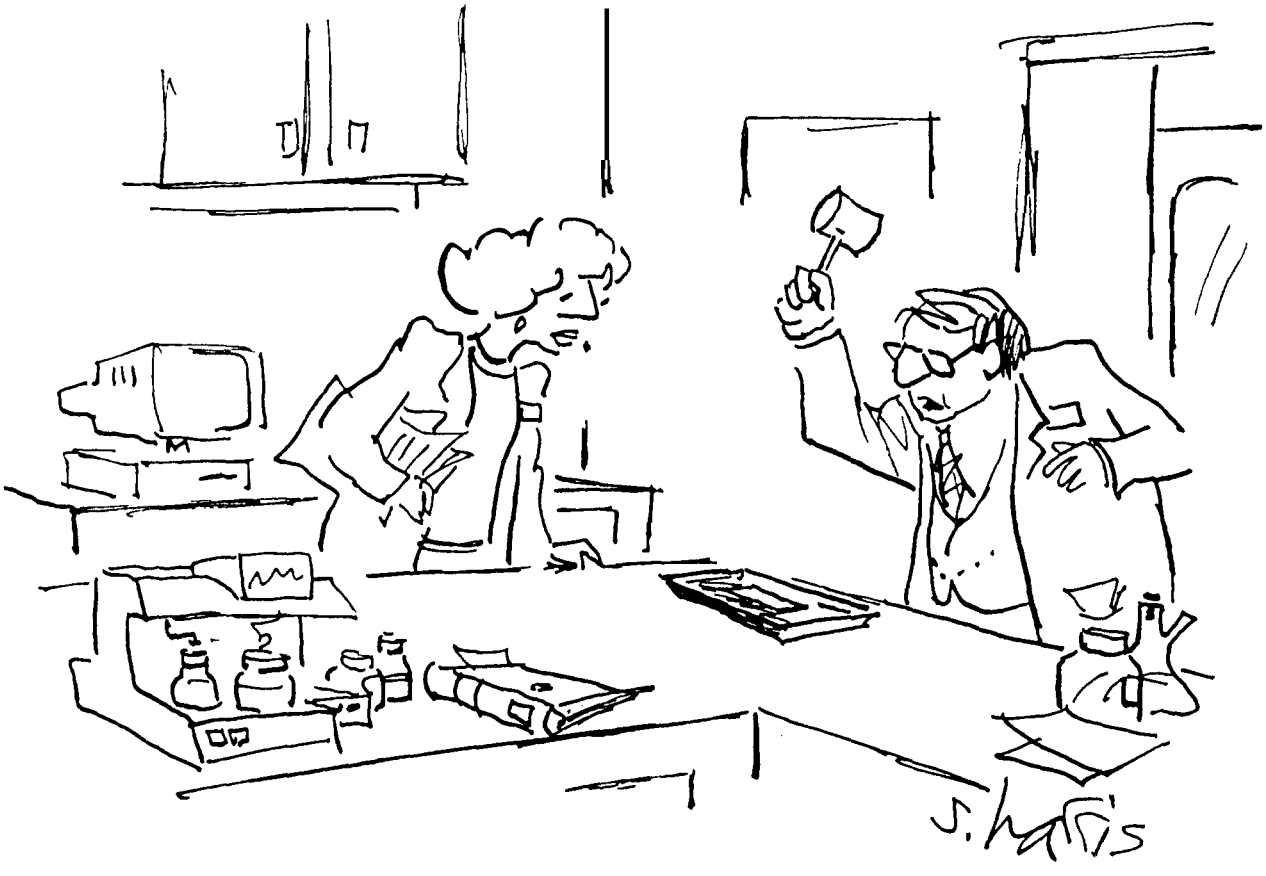
DIAGNOSTIC METHODS

In the future, science may develop a small device, such as the "tricorder" used in the TV series *Star Trek*, that physicians can pass over the body of a sick person to identify the cause of a disease. Such methods are far in the future, and current techniques used to identify bacteria and susceptibility patterns are "traditional methods" that have been developed over the last century. Newer methods that involve techniques from molecular biology and modern instrumentation—not immediately at the level of *Star Trek*—promise to make identification and characterization faster and more certain.

Traditional Methods for the Identification of Bacteria

Some experts estimate that there may be a million different bacteria and that scientists have identified only one percent (10,000 species) of that total. Of those 10,000, only a fraction have been associated with human diseases.

When seeing a patient, a physician will ask questions, make observations, and perform tests to determine which bacteria are likely to be associated with an illness and to choose an antibiotic treatment. The physician may swab the throat in the case of a sore throat or obtain a sample of urine in the case of a urinary tract infection. The collected material on the swab or the urine can be stained with diagnostic dyes, such as the Gram stain (see chapter 2), and examined under a



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microscope. Distinctive shapes and staining properties facilitate reliable preliminary rapid identification of the bacteria causing infection.

Collected samples may contain such low numbers of bacteria as to make finding them under the microscope difficult. The staining properties and shapes of the bacteria may not be unique and therefore not identifiable. The sample may contain a mixture of bacteria, as is common in faecal samples. To identify the bacteria in those cases, the physician sends a biological sample of some kind—a volume of blood ***or*** pus ***or*** other exudate, a scraping or swab from the throat or other orifice, a sample of urine or feces—to a microbiology laboratory.

In the laboratory, the sample is transferred to culture media specifically designed to encourage the growth of certain pathogenic bacteria and to prevent the growth of others such as commensal bacteria that may be present in samples from both healthy and sick individuals. The bacteria that are able to grow form visible colonies on agar-based media in a Petri dish or grow in broth so that the broth becomes turbid, as apple cider does when yeast grow in it. In both the collection and handling of the sample, health care personnel must be careful to avoid contamination with the bacteria that grow literally everywhere, on the patient's and physician's skin, on the surfaces of furniture and unsterilized devices in the examining room, and on apparatus in the diagnostic laboratory.

Microbiologists can sometimes look at and smell the colonies or liquid cultures and, based

on their knowledge and experience, identify the bacteria in the sample. They may be able to dismiss some bacteria from further consideration by recognizing them as contaminants. Iterative tests with more selective media and biochemical tests may be used for more specific identification.

Culturing and identification take time. The shigella that might be present in a fecal sample, or the *Escherichia coli* that frequently cause urinary tract infections, grow quickly, forming colonies in 24 hours or so, and a laboratory would probably identify them in one or two days. *Mycobacterium tuberculosis* grows far more slowly, and six weeks may pass before traditional methods can be used to identify it.

Identifying the bacteria is often critical for choosing the most appropriate antibiotic therapy because some antibiotics work better against certain bacteria. But identification does not provide information about whether the bacteria are resistant to the antibiotic or susceptible to it. "Susceptibility tests" are used to determine that.

Traditional Susceptibility Tests

Information about antibiotic-resistance/susceptibility is developed by testing the bacteria isolated from the infection against six to 12 different antibiotics, or more if necessary. The results from these tests may support the use of the antibiotic that was empirically selected by the physician, indicate that other antibiotics would work as well, or show that the disease-causing bacteria are resistant to the antibiotic empirically chosen.

Jorgensen (1995) describes four methods that are currently used to determine the antibiotic susceptibility or resistance of bacteria: 1) disk diffusion tests, 2) broth dilution tests, 3) agar dilution tests, and 4) agar gradient methods.

Disk diffusion tests

Disk diffusion tests measure the size of a clear area of no bacterial growth around a sterile paper disk containing antibiotic. The size of this area, called the "zone of inhibition," can be measured and reported directly, or the measurement can be compared to criteria established by the National Committee for Clinical Laboratory Standards

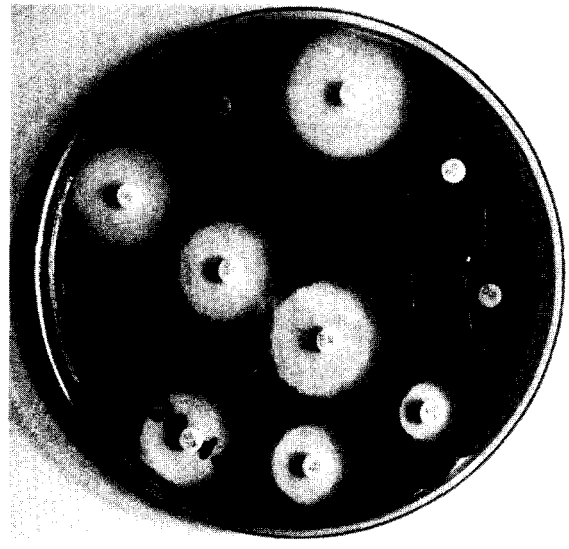


Photo of a disk diffusion (Kirby-Bauer) susceptibility test plate. Courtesy of James H. Jorgensen, University of Texas Health Science Center, San Antonio, TX, 7995.

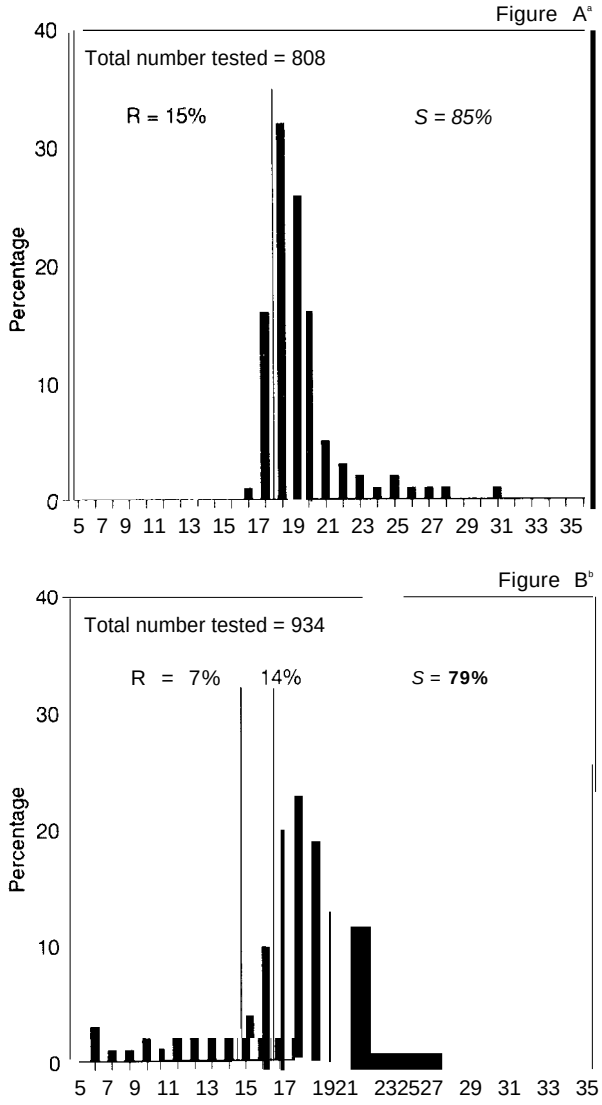
(NCCLS) to classify the bacteria as susceptible, intermediate or resistant (S, I, or R). These tests are well standardized for certain bacteria and may be highly reproducible. However, disk tests are influenced by many laboratory variables that can limit accuracy unless tightly controlled.

O'Brien (1994), who initiated and runs WHONET, the World Health Organization-sponsored surveillance system for antibiotic-resistant bacteria, emphasizes the importance of requiring laboratories to report raw data about the size of the zones of inhibition (figures 6-1 and 6-2) to surveillance organizations. While laboratories in Europe and North America are consistent in their measurement and reporting of the diameters of zones of inhibition around antibiotic disks, they interpret the meaning of the measurements differently (figure 6-l). Therefore, data reported as zones of inhibition rather than as interpretations are necessary to make any valid international comparisons about the prevalence of antibiotic-resistant bacteria.

Broth dilution tests

Dilution tests measure the concentration of antibiotic that is necessary to prevent the growth of bacteria. In these tests, known amounts of bacteria are deposited into small test tubes containing

FIGURE 6-1: Histograms of the Range of Zone Diameters for Enterocci Tested Against Vancomycin, During 1992



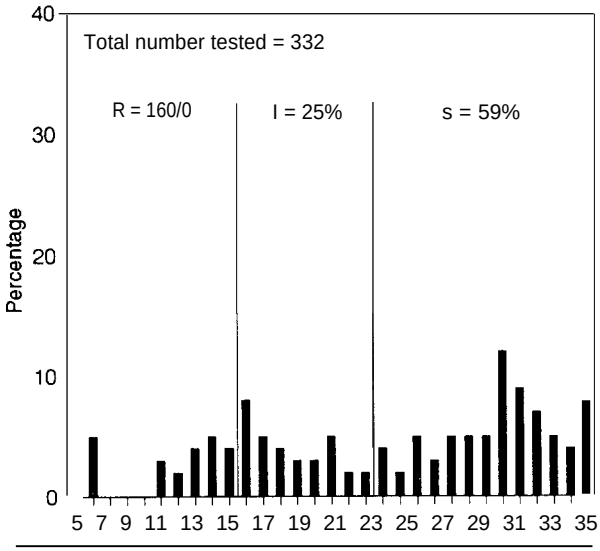
[a] Figure A represents a center in Europe (Center 1).

[b] Figure B represents a center in North America (Center 5).

NOTE: European and North American centers measured similar zones of inhibition, illustrating the reproducibility of the methods. However, the use of different break points in the two centers would result in the centers reporting different percentages of resistant organisms. Even if the laboratory data were identical, the centers would' report different percentages of resistant organisms. This example demonstrates the importance of reporting raw data for making comparisons between laboratories.

SOURCE: WHONET, 1994.

FIGURE 6-2: *Klebsiella pneumoniae:* S, I, R Distribution Cefotaxime Susceptibility Data



NOTE: This histogram illustrates the ambiguity of setting breakpoints for classifying bacteria as susceptible, intermediate, or resistant. In particular, the breakpoint for the division between resistant and intermediate appears to fall at a peak in measured zones of inhibition.

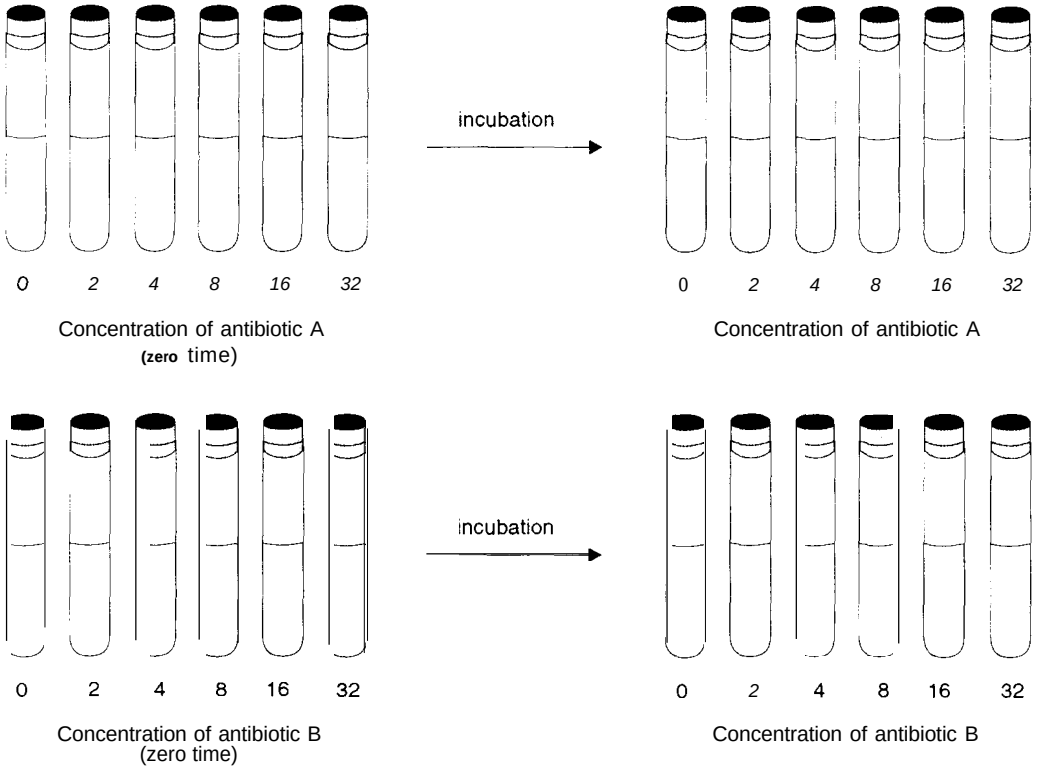
SOURCE: WHONET, 1994

1 to 2 milliliters (a teaspoonful is about 5 milliliters) of sterile nutrient growth medium ("broth") containing different concentrations of antibiotic (figure 6-3). The lowest concentration of antibiotic that prevents growth of the bacteria defines the "Minimum Inhibitory Concentration" (MIC).

While the MIC provides information about the concentration that will inhibit the growth of a bacterium, it does not say whether that concentration can be reached in the treated patient or what dose of antibiotics is needed to reach the critical concentration. Interpretive guidelines provided by NCCLS publications help clinical microbiologists and physicians interpret MICs as clinical categories of S ("susceptible"), I ("intermediate"), and R ("resistant").

A disadvantage of this method is the large number of test tubes and racks and large volumes of media that are required. To test a single bacterial culture against six antibiotics would require 42,48, or 54 tubes, depending on the lowest concentration used. The miniaturization of this

FIGURE 6-3: Broth Dilution Test



NOTE: In both A and B, a small measured volume of bacterial culture is added to each test tube at time zero, Following incubation (the time of Incubation depends on the growth characteristics of the bacteria), the test tubes in which bacteria were able to grow are turbid (the first three tubes in A and all tubes in B). The absence of growth in the last three tubes that contain antibiotic A indicates that the bacteria are killed or inhibited by concentrations of A equal to 8 units or more, Growth in all tubes that contain antibiotic B indicates that the bacteria are resistant to all tested concentrations of antibiotic B

SOURCE: Office of Technology Assessment, 1995.

method with microdilution trays solved that problem. The broth *micro* dilution test is currently the most popular antibiotic sensitivity test in the U.S. (table 6-I; the test using test tubes is called the "broth *macro* dilution test"). The small size of the wells and the small volumes, about 0.1 milliliter (about a drop from an eye-dropper), require that some viewing device be used to determine which of the wells in the test plate are clear and which are turbid. There are a number of commercial devices that make that determination, and some plot out the MICs from the tests.

To hold down costs and reduce the space needed for incubation of test cultures, many laboratories do not use the entire series of dilutions

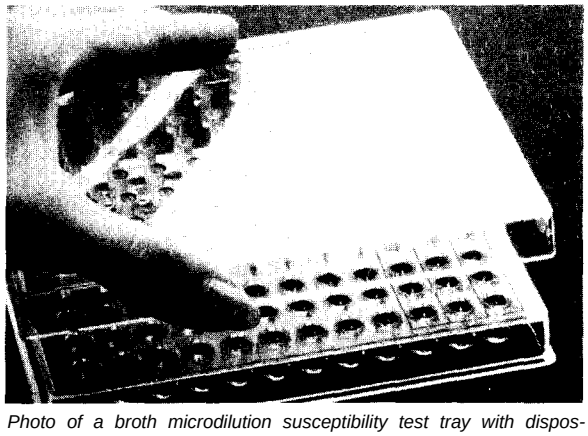


Photo of a broth microdilution susceptibility test tray with disposable inoculator.
Courtesy of James H. Jorgensen, University of Texas Health Science Center, Sari Antonio, TX, 7995,

TABLE 6-1: Most Commonly Used Antibiotic Susceptibility Testing Methods

Testing method	Percent of laboratories reporting routine use
Broth macrodilution	1.8
Broth microdilution	
Commercially prepared	46.2
User prepared	**0.4**
Agar dilution	**0.2**
Disk diffusion	31.8
Rapid automated	19,7

SOURCE: Jorgensen, 1995. From data collected in a 1991 Proficiency Survey of 3414 laboratories conducted by the College of American Pathologists.

as diagramed on figure 6-3. Instead, based on the NCCLS interpretive criteria, only two to three dilutions of each antibiotic are used. One of the dilutions is set to match the "break-point" that defines the division between the resistant and intermediate response; another dilution matches the concentration that defines the break-point between the intermediate and susceptible responses (see figure 6-2 for examples of break-points using disk diffusion tests). When only two or three dilutions are used for each antibiotic, the tests provide only an estimate rather than a quantitative measurement of the MIC. The true break-point might be somewhat different from the guidelines, and this fact can cause errors in classifying the bacteria as resistant or susceptible.

Agar dilution tests

Agar dilution tests are similar to the broth dilution tests in that they measure the MIC. In these tests, a small volume of a bacterial suspension, usually 1–2 microliters, is transferred to each of a series of agar plates containing known concentrations of antibiotics. Multi-prong devices are used to transfer approximately 100 colonies at one time.

Antibiotic gradient susceptibility test methods

Two commercial methods, the Etest[1] (AB BIODISK, Solna, Sweden) and the Spiral Gradient Endpoint System (Spiral Biotech Inc., Bethesda, Maryland), use antibiotic concentration gradients on agar plates. Both tests establish MICs that compare closely with those determined in the disk diffusion or broth dilution tests, and both are useful for testing anaerobic and other hard-to-grow bacteria.

The Etest has been cleared by the FDA for clinical use in the U.S. The Spiral Gradient End-

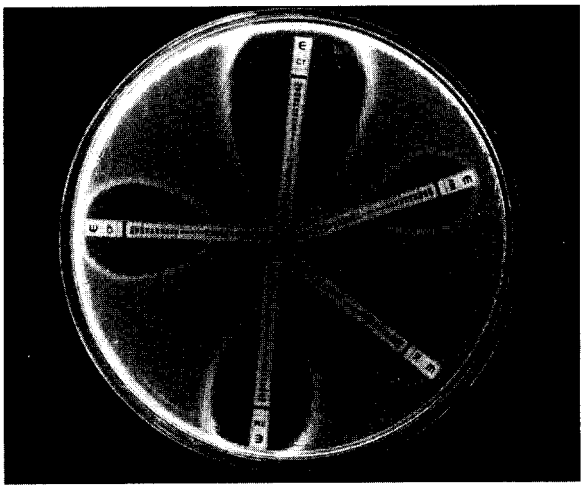


Photo of five Etest strips on the surface *of an agar plate. Intersection of the growth ellipses with the strips indicate the MICs. Courtesy of James H. Jorgensen,* University of Texas Health *Science Center, San Antonio, TX, 1995.*

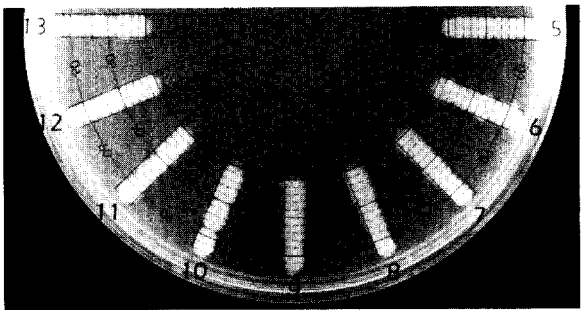


Photo of the Spiral Assay System Susceptibility Test. Courtesy of Spiral Biotech, Inc., Bethesda, MD, 1995.

1 OTA mention of a company or product does not constitute an endorsement. Furthermore, companies and products are mentioned as examples; competing companies and products exist.

point System has not yet been cleared by the FDA for clinical use.

These tests may have a special advantage for resistance surveillance because they have a continuous concentration gradient and are able to show subtle changes in susceptibility, and the wide concentration gradients of these tests cover the MIC ranges of susceptibility of a wide variety of pathogens and allow both low-level and high-level resistance to be detected. The Etest is reportedly easy to use in most laboratory settings and requires no complicated procedures.

Modifications of Traditional Methods To Shorten Times Necessary To Obtain Results

The four methods discussed require at least overnight incubation to obtain results. That time can be shortened to four to 10 hours for certain antibiotics and organisms by using optical devices (sometimes coupled with fluorescent indicators) more sensitive than the human eye to detect growth in microdilution tubes. Two commercially available automated systems can produce results in four to 10 hours.

The AutoSCAN Walk/Away (Dade Microscan, USA, Miami, Florida) uses standard microdilution trays that are inoculated in the standard way and placed in an automated incubator that uses a fluorometer to detect the presence or absence of growth at different antibiotic concentrations. The Vitek System (bioMerieux Vitek, Hazelwood, Missouri) was developed by NASA to diagnose urinary tract infections in astronauts in space in the 1970s. It uses credit-card size reagent cards, each of which has 30 tiny wells for the testing of different antibiotic concentrations, and the assays can be completed in three to 10 hours. While both systems provide rapid results, each requires backup cultures and other tests in case of power or mechanical failures.

In some cases, the automated machines can fail to detect resistance. To deal with this problem, manufacturers of both of these instruments have developed computer software that reviews the results to identify those that may be false. Some of these systems can also identify unexpected resistance patterns and offer suggestions for antibiotic treatment (Jorgensen, 1993). Computer analysis of the test results can also be linked to the hospital pharmacy's computer to alert the pharmacy personnel when the wrong antibiotic therapy is being used. As discussed in chapter 4, computer networks such as this can improve patient care and reduce costs.

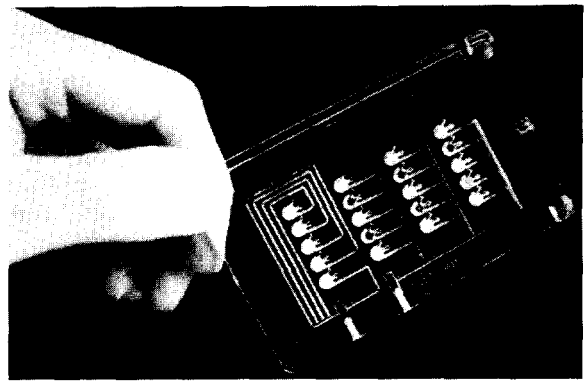


Photo of bioMerieux Vitek susceptibility testing reagent card. It was originally developed by NASA to diagnose urinary tract infections in astronauts in space and had to be very small. Courtesy of James H. Jorgensen, University of Texas Health Science Center, San Antonio, TX, 1995.

Summary of the Test Methods

Table 6-1 shows the reported frequency of use of the various test methods in a survey of American laboratories, and table 6-2 provides information about the relative costs of the most commonly used methods. None of the methods differs very much in labor costs. Based on the costs of equipment and supplies, the disk diffusion method is the least costly. O'Brien (1994) argues that it can also be the most informative under most conditions because the sizes of the zones of inhibition (see photograph) provide raw data that have not been subject to interpretation, and zone of inhibition information is more quantitative than broth dilution tests that are sometimes based on only one or two dilutions.

Will Faster Tests Make a Difference?

A test result that shows that bacteria are resistant to the empirically chosen antibiotic will certainly cause the physician to substitute another antibi-

Method or instrument	Test format	Means of growth detection/ endpoint determination/time	Equipment required	Approximate cost of equipment	Approximate cost/test*
Broth microdilution (prepared in-laboratory)	96-well plastic microtiter trays	Visual determination of MICs by turbidity; 18–24 hours	Tray dispenser, manual reader	$35,000	$6–7
Broth microdilution (commercial frozen or dried trays)	96-well plastic microtiter trays	Visual determination or automated reader interpretation of MICs; 18–24 hours	Choice of manual reader or auto-reader	$500 $50,000	$7–9
Disk diffusion	6–12 disks on 100–150 mm petri plates	Visual measurement of zones of inhibition; suscept. categories; 16–18 hours	None (only standard lab incubator)	None	$1.50–4
Etest	1–5 strips on 100–150 mm petri plates	Visual determination of MICs; 16–18 hours	None (only standard lab incubator)	None	$3–11
Dade MicroScan WalkAway	96-well plastic microtiter trays	Fluorogenic substrate auto-incubator/ reader MICs; 3.5–15 hours	Auto-incubator/reader	$85,000 $125,000	$10–12
bioMerieux Vitek	30–45-well plastic cards	Kinetic turbidimetric MICs or categories; 4–15 hours	Auto-inoculator/ incubator/reader	$40,000 $152,000	$4–6

* Includes cost of consumable supplies only; labor requirements do not differ substantially between methods.

SOURCE: J.H. Jorgensen. March 1995. Current and future phenotypic methods for detection of resistant bacteria. Report prepared for the U.S. Congress, Office of Technology Assessment.

otic if the patient is not improving. Sometimes, however, the patient improves despite the presence of apparently resistant bacteria. This can occur because the patient's immune system is successfully controlling the bacteria, or because the antibiotic reached a higher concentration in the patient's body than in the laboratory test, so that the bacteria were killed or inhibited.

Up to 40 percent of antibiotic therapy was inappropriate as judged by a comparison of physicians' prescriptions to an analysis of the laboratory results for bacterial identification and antibiotic susceptibility tests (see, for example, Jorgensen and Matsen, 1987). While older reports in the literature (see Edwards, Levin, Balogtas, et al., 1973) indicated that physicians pay little attention to microbiology test results, more recent publications (Doern, Scott, and Rashad, 1982; Weinstein, Murphy, Reller, et al., 1983; Jorgensen and Matsen, 1987) indicate that some physicians do modify their prescriptions upon receiving additional laboratory information. In particular, rapid susceptibility tests, which can be completed in four to 10 hours, resulted in more appropriate therapy, and Doern, Vautour, Gaudet, et al. (1994) found that rapid tests resulted in fewer additional laboratory tests, fewer invasive procedures, shortened time in intensive care, and reduced mortality.

Physicians typically receive the results of antibiotic susceptibility tests on the morning of the second or third day after specimens are submitted to the laboratory. The faster methods produce the results more quickly, but unless the physicians and nursing staff are prepared to use the information at the earlier time, it will not be considered until the next morning. In this case, technological improvements can only be useful if accompanied by changes in habits.

Jorgensen (1995) discusses another obstacle to the use of rapid methods. Laboratory managers often confirm the results of the faster methods with backup tests using the older, slower methods. However, this requires performing the tests more than once and therefore increases costs. Trade-offs must be made among the objectives of speeding up the process, ensuring accuracy by performing backup tests, and saving money.

New Technologies for Identifying Bacteria

Antigen Tests

Antigen tests use antibodies to recognize specific molecules on or in bacterial or other cells. For instance, the home pregnancy test detects antigens that are produced only during pregnancy.

There are many versions of antigen tests to detect the presence of strep A bacteria in sore throats, but the usefulness of these tests is limited by low sensitivity. Traditional cultures are still recommended when tests are negative. Antigen tests are also available to detect *Clostridium difficile* in patients with diarrhea and to determine the bacterial cause of meningitis.

Methicillin-resistant *Staphylococcus aureus* (MRSA) presents identification problems because it and all other *S. aureus* grow slowly. Further, its identification is usually accomplished by a specific test for protein antigens on its surface, and these tests failed to identify between 1 and 25 percent of *S. aureus*. Kuusela, Hilden, Savolainen, et al. (1994) discovered another protein on the surface of *S. aureus* and developed a test for it that detects both methicillin-susceptible *S. aureus* and MRSA.

Tests which Directly Measure the Presence of a Bacterial or Antibiotic Resistance Gene

Tests which directly measure the presence of a bacterial gene (discussion of tests for antibiotic resistance genes follows) are fundamentally different from the traditional tests, which measure a property of an organism such as its ability to grow in the presence of a certain concentration of antibiotic. The new gene tests bring with them a new set of considerations: A bacterium might contain a gene for resistance, but not "express" it under the conditions of the traditional diagnostic tests, or a resistance gene may have undergone a mutation that does not affect its function but that makes its presence undetectable, or the genes of dead bacteria may be detected with DNA tests.

For example, samples from a patient who is being successfully treated with anti-TB drugs often test positive in DNA tests, but negative in culture-based tests that rely on growing the organism. These are problems that must be considered in designing new genetic tests and using them in clinical practice.

One huge advantage of tests that measure the presence of a bacterial gene is that they are quick; many tests take only a few hours or less. Another advantage is that they generally have much higher sensitivity than the antigen and other enzymatic tests described above, although in some cases the sensitivity is not as high as that of traditional culture methods. The speed combined with the sensitivity is very useful. However, some tests require culturing, i.e., the growing of bacteria from the clinical samples, before the genetic test can be performed. The culturing requirement adds time to the process. To date there exists no test so rapid that it will confirm bacterial identification and susceptibility before a patient leaves a physician's office. The development of faster and more susceptible genetically based tests for bacteria started in the early 1980s, but most are still not available for routine use. Nevertheless, some of these tests, such as those that are able to diagnose tuberculosis in a few hours instead of a few weeks, represent a significant technological advancement that has improved clinical practice.

DNA probe assays

Single-stranded fragments of DNA or RNA that are complementary to a target DNA or RNA sequence will form a double-stranded molecule, known as a "stable hybrid," under certain reaction conditions. Diagnostic fragments, or probes, which will bind to target DNAs or RNAs, are labeled with enzymes or dyes so that the binding of the probe to the target can be detected.

At the present time, several commercial DNA probe tests in clinical use are manufactured by Gen-Probe, Inc. (San Diego, California), GeneTrak (Framingham, Massachusetts), Ortho Diagnostic Systems (Raritan, New Jersey), and others. Some of these tests are designed to confirm the identification of cultivated colonies, such as tests for *M. tuberculosis*, *M. avium* (an important pathogen in patients with AIDS), and *Neisseria gonorrheae* (the agent of gonorrhea). Other tests can be used for the direct detection of bacteria in clinical samples, such as Neisseria, *Chlamydia trachomatis* (an agent of urethritis, cervicitis, and pelvic inflammatory disease) and *S. pyogenes* (a cause of suppurative tonsillitis or "strep throat"). These are organisms that for the most part are difficult or slow to cultivate and identify in the laboratory. The tests require approximately two to four hours to complete and cost the patient approximately $20–40 per test.

One important disadvantage of probe-based methods to date has been their low sensitivity compared to culture-based methods. Probe assays for *M. pneumoniae* (an agent of atypical or "walking" pneumonia) and *Legionella pneumophilia* (the agent of Legionnaire's Disease) are no longer much used, primarily because of this problem. New technologies in development, which provide the ability to amplify probe or probe-linked signals after binding to the target, may help increase the sensitivity of these tests.

One promising probe-based test that does have adequate sensitivity is a rapid direct DNA probe test from Gen-Probe that can identify Group A Streptococcus directly from throat swabs. In comparative studies, test results agreed closely with those from older and slower tests (see, for example, Rippin, et al., 1994; Heiter and Bourbeau, 1993), unlike the quick antigen strep tests described above. However, Heiter and Bourbeau conclude that because this test requires several instruments not routinely found in doctors' offices and because it still requires two hours, the test will not be useful for point-of-care testing in doctors' offices or emergency room clinics.

Target amplification methods

One of the most promising approaches for increasing the sensitivity of probe-based DNA tests is to amplify the target DNA sequence through such methods as polymerase chain reaction (PCR), which can rapidly generate millions

of copies of bacterial or resistance gene DNA or RNA sequences. PCR requires identifying and synthesizing short sequences complementary to the target gene that act as "primers" for the synthesis of the DNA. It is relatively easy to synthesize millions of these short sequences, but it would be difficult to synthesize larger pieces of DNA. Starting with as little as one strand of DNA from the sample, PCR uses enzymes to elongate the "primers" into full copies of the DNA. PCR can generate millions of copies of a particular DNA in hours.

Species-specific PCR detection assays have been developed for at least 50 different bacterial pathogens, and specific sequences are available from a much larger number of species, for which PCR primers can be designed. However, only a few standardized kits for performing these tests on specific bacterial species are commercially available in the U.S. Among those kits that either have been cleared, or are nearing clearance, by the Food and Drug Administration are PCR assays for *C. trachomatis, N. gonorrheae*, and *M. tuberculosis*. Even without a commercially available standardized kit, the tests can still be set up individually by service labs. However, there are several disadvantages to performing these tests without using a standard kit. First, most of these assays do not perform as well in detecting bacteria in clinical samples as they do in purified cultures; suboptimal sample preparation procedures and reaction conditions are probably to blame. Second, unless physical, chemical, or enzymatic precautions are in place, PCR and other target amplification methods are easily jeopardized by contaminating nucleic acid, either from prior amplification reactions or from positive clinical samples. Third, there is dramatic interlaboratory variability in the test results for the same group of clinical samples. Many of these problems may be solved by the availability of standardized commercial kits.

After the nucleic acid is isolated and amplified by a technique such as PCR, the nucleic acid can be sequenced to identify the organism. Automated sequencers marketed by Applied Biosystems can determine 48 independent DNA sequences of 400–500 nucleotides in length in approximately 8 hours, and speed and sequence length capabilities are continually being improved. Automated sequencing systems require an initial investment of approximately $55,000 (Molecular Dynamics) to $125,000 (Applied Biosystems, including sequence analysis software). It is estimated that identification of a single bacterial isolate with an automated procedure will cost approximately $75.

Another way to identify the organism is to bind the nucleic acid to probes that recognize specific sequences. Currently, sequences prepared from specific reference strains of bacteria are used. New strategies are expected to use random sequences of nucleic acid bound in orderly arrays on micro-scale photolithographic silicon chips, and the nucleic acid can be identified by determining which probes bind to it. Because of the microscopic scale of these tests, the bound nucleic acid must be detected with a laser confocal microscope. This approach has already been shown to be useful for the detection of single base pair mutations in the human immunodeficiency virus. This technology offers significant potential for rapid sequence determination of specific gene targets and for the detection of specific identifying signature sequences or antibiotic-resistance-associated sequences. First-generation chip-based sequencing systems may be available for research by 1996.

Using rapid DNA tests to diagnose tuberculosis

Diagnosing tuberculosis is difficult because it has many different clinical manifestations. Moreover, many physicians were not trained to recognize tuberculosis because its prevalence was decreasing until about 10 years ago. The recent resurgence of this disease is a huge problem, both in the United States and around the world, and rapid diagnosis is critical so that patients can be treated before they pass this highly infectious disease to others. Quick determination of the susceptibility of the infecting organism is also becoming increasingly important because many

drugs are inactive against some of the multi-resistant strains of tuberculosis.

The tuberculin skin test is often used as the first diagnostic indication that a person has been infected with tuberculosis. A positive tuberculin skin test does not mean that the person has active disease, only that the person has been exposed to tuberculosis. Haas and Des Prez (1995) review studies of the interpretation of positive tuberculin skin tests in nursing homes which show that 3.8 percent of men who were tuberculin-positive on admission to nursing homes subsequently developed active disease, and that 11.6 percent of men who became positive while in the nursing home later developed the disease. The percentage developing active disease could be reduced to 0.2–0.3 percent with the prophylactic use of the antibiotic INH. However, the level of hepatic toxicity from INH was 3–4 percent, and there were other side effects. Deciding when to prescribe antibiotics for a patient with a positive skin test but no other symptoms is very complicated because the toxicity of the drug must be weighed against the probability that the patient will develop tuberculosis. The same considerations apply to new diagnostic tests based on the detection of the DNA of *M. tuberculosis.*

Isolating the mycobacteria causing tuberculosis requires from three to eight weeks, and susceptibility testing by agar dilution methods requires another three to six weeks. Highly variable results have been observed between two different clinical laboratories using culture methods (Hewlett, Horn, and Alfalla, 1995). The identification and susceptibility testing of drug-resistant TB can be significantly hastened by using the BACTEC radiometric method, but the time required is still 20 days or more. Recent data on the Etest for susceptibility testing of mycobacteria suggest that MIC values can be obtained in five to 10 days, a significant improvement over current methods (Wanger and Mills, 1995).

With PCR and probe-based DNA tests, physicians will have the ability to identify mycobacteria in the sputum of patients within a few hours to a few days. All tests that are currently cleared by the FDA require some culturing of the clinical sample, but newer tests in development will allow identification of mycobacteria directly from clinical samples. These tests are used in many other countries, including much of Europe. Some laboratories are promoting clinical use of PCR tests in the U.S. Macher and Goosby (1995) document a difficulty in interpretation of PCR tests in the absence of other clinical signs of tuberculosis. On the basis of two (out of three) positive PCR tests, the patient received antituberculosis chemotherapy and was placed in isolation. Later, six cultures turned out to be negative for tuberculosis, and the patient was taken off drugs for active tuberculosis and placed on INH alone for preventive therapy. This case study indicates that the DNA probe tests might be too sensitive: they might detect non-viable mycobacteria from a previous exposure. This result is comparable to a positive tuberculin skin test, which, as discussed above, indicates past exposure to mycobacteria but does not necessarily signify active tuberculosis.

New Technologies for Detecting Antibiotic Resistance

The increasing prevalence of antibiotic-resistant bacteria is leading manufacturers to develop tests specifically to identify resistant strains. In general, these tests are designed to produce results in a few hours. Discrepancies may arise between the results of old and new methods. The older methods directly measure whether an organism expresses resistance and can grow in the presence of an antibiotic. Some of the newer methods indicate whether an organism has a gene encoding for resistance. However, the organism may not "express" this resistance even if it has the gene. In some cases, it is unknown whether the presence of the gene or the expression of the gene under laboratory conditions is the more important predictor of clinical outcome.

Enzymatic Tests

Enzymatic tests can directly measure the presence of an enzyme that confers antibiotic resistance, such as β-lactamases that inactivate

penicillins and other β-lactam antibiotics and the enzyme that inactivates chloramphenicol. The detection of the β-lactamases requires only a few minutes (Stratton and Cooksey, 1990), but it is limited to only a few bacterial species. Moreover, it does not detect penicillin resistance caused by other mechanisms, such as the production of modified penicillin binding proteins. The test for the chloramphenicol inactivating enzyme requires one to two hours and can be used to detect the most common form of chloramphenicol resistance, but it has decreasing utility because of the declining use of this antibiotic.

Tests Based on Indicator Dyes or Light-Producing Enzymes

Some tests add indicator dyes to a bacterial culture and then detect the presence of living organisms by a color change in the indicator dye. An example is the Crystal MRSA Rapid ID test from Beckton Dickinson. This test, which can detect MRSA in four hours in cultured bacteria, uses an indicator dye that can be observed under an ultraviolet light source in the absence of oxygen. In this test, three samples of bacteria are incubated with the indicator dye. In addition, one of the samples is incubated with oxacillin (a semi-synthetic penicillin similar to methicillin) and one of the samples is incubated with vancomycin. If the bacteria survive, they will use the oxygen in the samples and the dye changes color. If the sample contains MRSA, the organism will survive in the presence of oxacillin but not in the presence of vancomycin. If the organism is susceptible to oxacillin, it will not survive either antibiotic. The test, which costs about five dollars, does not require expensive instrumentation. Kohner, Kolbert, Geha, et al. (1994) found that this system is an effective rapid screening method for MRSA but has poor performance for coagulase-negative Staphylococci, which often present a greater diagnostic dilemma.

A more complicated test for multiresistant tuberculosis is currently in very early development (Jacobs, Barletta, Udani, et al., 1993). In this test, the gene for the light-producing enzyme from fireflies was cloned into a virus that infects *M. tuberculosis*. The virus is added to a sample of sputum from the patient. The virus will infect any mycobacteria that are present. If the virus infects living mycobacteria, the viral DNA is activated, and the firefly enzyme will cause the culture to give off light. When antibiotics are added to the test, only resistant mycobacteria will support viral growth; susceptible ones will not, and susceptible cultures will not light up. Thus susceptibility can be determined. Research is currently underway to determine if this test can measure as few as 100 live *M. tuberculosis* bacteria, and would therefore work directly on patient samples in a few hours (Jacobs, NIH Grant R01AI27235). However, this sensitivity may be difficult or impossible to achieve because of background signals in the sample.[2]

DNA-Based Methods for Testing Antibiotic Resistance

Current susceptibility patterns suggest that rifampin resistance in *M. tuberculosis* can be used as a predictive marker of multidrug resistance. In general, surveillance indicates that resistance to rifampin correlates well with resistance to three or more antituberculosis drugs. Furthermore, virtually all of the highly resistant mycobacterial strains (resistant to greater than five drugs) are rifampin-resistant. However, this may change in the future if *M. tuberculosis* undergoes further genetic mutation.

PCR tests are in development to detect rifampin resistance in *M. tuberculosis* caused by the *rpo*B gene. The use of the signature sequences in the *rpo*B gene assumes that there are not significant numbers of rifampin-resistant *M. tuberculosis* strains in the community with other, uncharacterized *rpo*B mutations in the gene.

[2] All samples "glow in the dark"—some background signals are detected. This test will only achieve high sensitivity if the signal from the firefly enzyme is significantly larger than the background signal.

MRSAs are currently identified by using the traditional tests discussed in the first part of this chapter. The performance of these tests may be variable. Factors such as the inoculum size, incubation time and temperature, pH of the medium, salt concentration of the medium, and prior exposure to β-lactam antibiotics all influence the expression of resistance. To complicate matters further, only some bacteria in a culture may express methicillin resistance, even if all have the gene. Taking into account these factors, the National Committee for Clinical Laboratory Standards (NCCLS) has recommended guidelines to optimize the detection of resistance. However, occasional organisms have been isolated that are difficult to characterize by these methods. The results produced by various methods of disk diffusion and those from agar dilution methods are often not consistent. In addition, it is difficult to separate organisms that are highly resistant due to overproduction of β-lactamase from organisms that have the *mec*A gene encoding for an altered penicillin binding protein. Organisms resistant due to the *mec*A gene often require vancomycin therapy, while organisms resistant due to overproduction of β-lactamase might actually respond better to treatment with β-lactam antibiotic/β-lactamase inhibitor combinations than vancomycin.

PCR and DNA-probe techniques have now been developed to identify the *mec*A gene. In general, the studies to date show a high degree of correlation between traditional and DNA-based tests and allow accurate classification of highly resistant and borderline resistant strains.

Guidelines for interpretation of the *mecA* detection result will need to be formally addressed as more laboratories begin to use this and other genetic methods. Proposals have been made to regard *mecA*-positive organisms (both coagulase-negative staphylococci and *S. aureus*) as intrinsically resistant to all antibiotics except vancomycin and to report immediately all *mecA*-positive results, which can be available well before results from traditional methods. There are situations where the *mecA*-positive organism does not express resistance clinically and may respond to β-lactam therapy. It is important to document these cases carefully to avoid unnecessary use or overuse of vancomycin. Nevertheless, all *mecA*-positive organisms may be highly resistant if the organism expresses the *mecA* gene. This may lead to treatment failures if β-lactam antibiotics are chosen.

Surveillance and DNA-based diagnostics

Surveillance of genetic mutations in bacteria will be essential in the use of new DNA diagnostics, which measure the presence of specific genetic sequences. Mutations might alter these sequences, or new genes conferring resistance may spread. For example, widespread surveillance efforts are necessary to insure that signature sequences represent the majority of mutations in the *rpo*B gene that confer rifampin resistance in *M. tuberculosis*.

Regulation of Diagnostic Tests

The Clinical Laboratory Improvement Amendments (CLIA '88) were passed by Congress to regulate the quality of diagnostic testing. Regulations under CLIA, which became effective in September of 1992, require all clinical laboratories that perform certain diagnostic tests to register with the federal government and perform quality control tests and document quality assurance. However, certain tests are "waived" under CLIA; this means that the test can be performed in any physician's office, whether or not the office is registered under CLIA. Other tests, generally the more complex ones, can be performed only in offices that comply with the CLIA regulations for laboratories.

The CLIA regulations may be a disincentive to performing tests. Complying with them increases the cost of testing and may delay results. For example, physicians may choose not to register their offices under CLIA and will therefore be compelled to send out numerous tests that they formerly performed. This may result in the performance of fewer diagnostic tests, which could contribute to the overuse of antibiotics. A physician might decide that it is

easier and more cost-effective to prescribe antibiotics for all sore throats rather than perform throat cultures. However, this negative potential consequence of the CLIA regulations must be weighed against whatever positive effects they have had on the quality and consistency of testing that is done in the clinical laboratories that meet CLIA standards.

Getting New Tests to Market

The worst outcome for a sensitivity test is to indicate that bacteria are susceptible to an antibiotic when the antibiotic has no effect against that strain. Such an error, which can result in a patient's death, is called a "very major error" in testing. The second worst outcome is to report that bacteria are resistant to an antibiotic that is in fact effective against them. That error, which could result in treatment with a more toxic, more expensive antibiotic than necessary, is termed a "major error" (Jorgensen 1995).

It is impossible to design and perform tests that are completely error free. The manufacturers, the FDA, health care providers, and the public have to decide what levels of errors are acceptable. Often, new tests are compared with a "gold standard"—an older test that has been proved to be reliable. However, the "gold standard" is also not completely error free. Therefore it is sometimes difficult to interpret differences between a new test and a "gold standard." For example, culturing *M. tuberculosis* is considered the "gold standard" for the diagnosis of tuberculosis. However, Abe, et al. (1993) found that some patient samples were positive for *M. tuberculosis* by DNA-based techniques but negative when cultured; these patients had clinical signs of tuberculosis, including characteristic radiographs, clinical manifestations of the disease and/or clinical response to antituberculosis chemotherapy.

Two FDA centers are involved in approving test methods for antibiotic susceptibility. The FDA Center for Drug Evaluation and Research certifies that disks are available for each antibiotic on the market in the United States, and it assures the potency of the disks and that criteria for interpretation of the disk assays are available when an antibiotic goes on the market. The FDA Center for Devices and Radiological Health has responsibility for determining the safety and effectiveness of other devices and materials, including computer software, for susceptibility testing.

A new diagnostic device can be reviewed by FDA under two different procedures. A device or method that employs principles similar to those used by products already on the market and that requires an incubation period of 16 hours or more is reviewed under the "510(k) clearance" process. The performance of the new device or method is compared to the performance of the product already marketed to determine whether the two are "substantially equivalent." If they are, the new device or method is cleared for marketing without undergoing the more extensive procedures, known as "pre-market approval." The 510(k) process is also used when a manufacturer wants to add a new antibiotic to the battery of antibiotics already included in a test kit.

New diagnostic tests that are not "substantially equivalent" to any product on the market must submit an application for "pre-market approval" (PMA) to the FDA. Because the approval process under the PMA review is substantially more difficult, manufacturers have a disincentive to develop novel products.

Any device that requires less than 16 hours' incubation is required to undergo the pre-market approval process, which takes longer and is substantially more difficult to complete than the 510(k) clearance process. Jorgensen (1995) claims that there is no clear justification for the 16-hour incubation period serving as the cutoff between a 510(k) review and a PMA review because there is no indication that more rapid devices are inherently less accurate than others. The difference in the time required to obtain a 510(k) clearance, as opposed to a pre-market approval, is a matter of contention. According to Jorgensen (1995), the requirements for a 510(k) clearance have grown since 1990, and they are now approaching those required for a PMA. On

the other hand, FDA (1995) asserts that there have been marked improvements in the processing of 510(k) applications.

VACCINES

Perhaps the ultimate weapon against antibiotic-resistant bacteria is the development of vaccines and pre-emptive immunization. In concept, vaccines are simple. When a person receives an inoculation of a preparation of killed or attenuated ("weakened") disease-causing bacteria or virus, a component of such an agent, or a related organism that does not cause disease, the inoculated person's immune system will respond and produce antibodies to antigens on the injected materials. The immune system has a "memory." As a result, if the person is subsequently infected by the organism for which the vaccine was prepared, he or she will produce antibodies that can inactivate the agent and remove it from the body. "Natural immunity" is produced in a similar way; once a person has had a disease, the immune system recognizes the organism that caused it and eliminates it from the body.

In practice, preparation of the specific material for the inoculation—the antigen—can be difficult. Preparing it so that the production of antibody is stimulated without objectionable toxicity, either at the time of inoculation or later, may not be simple.

The success of *Haemophilus influenzae* type B (Hib) vaccines, which were introduced in 1988, demonstrates that antibacterial vaccines can be quite successful. Countering that great success is the more than 75 years' experience with an antituberculosis vaccine.

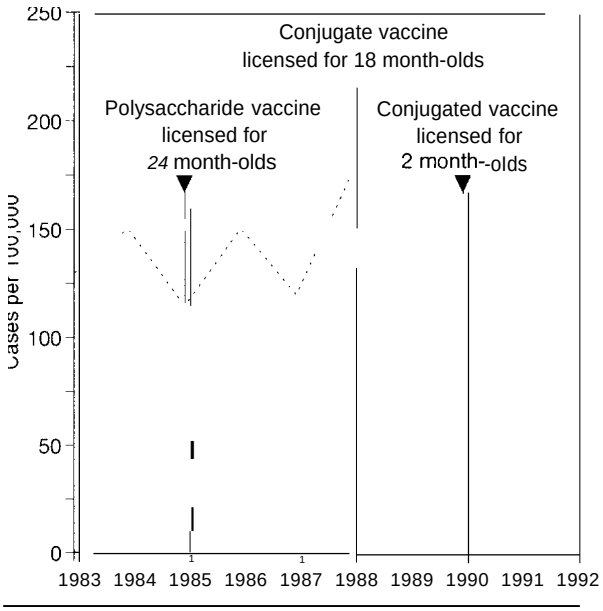
Hib Vaccines, a Success Story

Before the introduction of vaccines against it, Hib (*Haemophilus influenzae* type B) was the leading cause of invasive bacterial disease in children under five years of age, and it caused about 20,000 cases of meningitis and another 3,000 to 5,000 cases of invasive Hib disease annually. The mortality rate was 3 to 5 percent; moreover, up to 20 percent of the survivors of meningitis suffered hearing loss or mental retardation, and resistance to ampicillin was increasing (Adams, Deaver, Cochi, et al. 1993).

In 1993, five years after the introduction of Hib vaccines, a number of researchers published reports about the incidence of Hib diseases in children up to five years old. Those vaccinated with Hib vaccine generally had disease rates 80 to 90 percent below the rates seen in unvaccinated children (Wenger 1994). The rates of Hib meningitis began to fall in 1989, after the introduction of the vaccine, and they continued to fall through 1991 (the last year for which data were available). In contrast, the rates of meningitis from *Neisseria meningitidis* and *Streptococcus pneumonia* remained unchanged, ruling out a general decline in meningitis as the explanation for the Hib results. An unexpected result of the Hib vaccination program was a reduction in the number of children who carry Hib in their upper airways. That, in turn, reduced the number of children who could infect others, and the rates of Hib disease have fallen in both vaccinated and unvaccinated children.

A polysaccharide (a polymer of sugar molecules that is unique to the Hib bacteria) vaccine licensed in 1985 had no effect on the occurrence of invasive Hib disease in Los Angeles County (see figure 6-4) and, in fact, it was of little value in disease prevention. Three years later, a conjugate vaccine, prepared by chemically joining the polysaccharide to a protein that was known to stimulate antibody production, was licensed. This vaccine was very successful. Even when use of this vaccine was restricted to children older than 18 months (from 1988 through 1990), there was a drop in the Hib invasive disease rate in younger children. Vaccination of the older children had reduced infections of the younger ones, due to reduced transmission of the bacteria. Licensing of a vaccine for 2-month-old children in 1990 led to great reductions in the disease in Los Angeles County by 1992.

FIGURE 6-4: Invasive Hib Disease in Los Angeles County



SOURCE: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases. 1994. Annual Report, p. 1

BCG Vaccine, 75 Years' Experience

Albert Calmette and Camille Guerin at the Pasteur Institute in Paris first produced BCG as a vaccine for the prevention of TB. BCG is made from preparations of a live, attenuated strain of *M. bovis,* which is closely related to *M. tuberculosis,* and over 70 percent of children worldwide now receive the vaccine. It is compulsory in 64 countries and recommended in 118 others (OTA, 1993). People who have received this vaccine typically show a positive response to tuberculin skin tests. This is considered a great disadvantage in the U. S., where tuberculin skin tests are used to screen for exposure to tuberculosis.

Colditz, Brewer, Berkey, et al. (1994) reported the most thorough review of the efficacy of BCG vaccine. Their meta-analysis of the worldwide literature led to the conclusion that BCG reduced the risk of TB by about 50 percent, but the success rate vanes from batch to batch of the vaccine, which is prepared in different laboratories under different conditions around the world. The 50 percent effectiveness conclusion was challenged by a number of scientists (Benin, 1994; Wheeler, Rodrigues, and Diwan, 1994; Comstock, 1994), but the authors replied that ". . . meta-analysis shows that the preponderance of evidence reveals that BCG vaccine is effective in preventing TB" (Coldwitz, Brewer, Berkey, et al., 1994a).

The United States has never required the vaccine because of questions about its efficacy and its usefulness in a population with a low incidence of TB. In 1979 the Centers for Disease Control and Prevention (CDC) recommended the vaccine for health care workers in contact with TB patients, but CDC's 1988 policy statement reversed that recommendation because of the lack of evidence for increased TB among health care workers (OTA, 1993). CDC recommend BCG for members of high risk groups who have limited access to health care. However, the CDC believes that the rate of tuberculosis is so low in the general population of the U.S. that the advantages conferred by vaccination are outweighed by the disadvantage of being unable to screen the population by using the tuberculin skin test.

Vaccine Research

Successful vaccines are available for use against viral diseases such as measles, mumps, and rubella, and against bacterial diseases such as diphtheria, tetanus, and pertussis (whooping cough). Currently, researchers are pursuing new vaccines against bacterial pathogens, such as the Streptococcus species, *Staph. aureus* and *Helicobacter pylori,* which are common problems, in part because of high rates of antibiotic resistance.

Active Systemic Immunization

Active immunization is the process of administering specific microbial antigens that stimulate the host's immune system to produce protective antibodies. Active immunization can be systemic-the traditional method—or mucosal (discussed below). Systemic immunity is accomplished by injection, the result being long-lived production of circulating immunoglobulin G

(IgG) antibodies. For bacterial vaccines, polysaccharides from the outside capsule of the bacteria are generally employed, but as was seen with the Hib vaccines (Wenger, 1994), capsular polysaccharides alone do not always stimulate sufficient antibody production. To raise sufficient levels of antibodies, the polysaccharides may have to be conjugated with "carrier proteins," potent immunogens that provoke an immune system response to the entire complex (i.e., to polysaccharide antigen and protein carrier). The combination of polysaccharide and protein is called a "conjugate vaccine." Finding the proper carrier is one of the more difficult aspects of vaccine development, but four different proteins—all of bacterial origin—work well in Hib vaccines.

Streptococcus pneumoniae vaccines

Vaccine development is further complicated because different strains of the same bacteria have different polysaccharide antigens. For instance, *Streptococcus pneumoniae* has 84 distinct capsular polysaccharides. A vaccine that contains 23 different polysaccharides provides protection against 90 percent of invasive pneumococcal strains (Siber, 1994). That vaccine is 75 percent effective when administered to immunocompetent adults, and its wider use might prevent half of the 80,000 annual pneumococcal pneumonia deaths among older people (Medical World News, 1993). It is not, however, reliable in children under two years of age. For the vaccination of children, several companies are developing conjugated vaccines against the polysaccharides of the seven strains of pneumococcus that most commonly infect children, and these are currently undergoing human trials. In addition, researchers are investigating the possibility of using a polysaccharide that is common to all pneumococcus conjugated to one or more of several proteins that are common to all pneumococcus as vaccines, but there is no definitive evidence for their usefulness (Siber 1994).

Vaccines against otitis media

S. pneumonia is one of several bacteria that cause otitis media. That illness is so notorious that physicians who surveyed parents about their willingness to have their children immunized against the disease titled their report "The Surprisingly High Acceptability of Low-Efficacy Vaccines for Otitis Media..." (Wischnack, Jacobson, Poland, et al., 1995). Although no such vaccine is now in use, the interviewers asked about five hypothetical vaccines that had different efficiencies in disease prevention, and side effects that ranged from the temporary discomfort of a "shot" in all children to a few days of flu-like symptoms in up to half of vaccinated children. About half of the 601 interviewed parents would accept any vaccine if it would prevent three or more infections in the next six months. Parents were less accepting of vaccines with lower efficiencies and worse side effects. The authors of the study conclude that parents, even of children who have not had otitis media, are willing to accept some discomfort in their children to obtain protection against the disease and that parents' willingness is greater than the medical establishment's or FDA's.

A biotech firm, MicroCarb (Bethesda, Maryland), has licensed one vaccine against *Haemophilus influenza*, another cause of otitis media, to Pasteur Merieux Serums et Vaccines S.A. If this vaccine proves successful, it will be of value against both antibiotic susceptible and resistant *H. influenza,* which are increasingly common.

Staphylococcus aureus vaccines

Vaccines against *Staph. aureus,* which is often antibiotic resistant, would be helpful to patients at high risk for infection with this organism, including renal dialysis patients, or patients receiving prosthetic devices like hips or vascular grafts, which act as sites for infection (Univax, 1994). Researchers are pursuing vaccines made of capsular polysaccharide types 5 and 8, which would encompass 90 percent of Staphylococcus systemic infections. Recent research has shown that high levels of biologically active antibodies against *Staph. aureus* types 5 and 8 can be stimulated in human subjects when the antigens are combined with a protein from *P. aeruginosa* as

the carrier (Fatton, et al., 1990; Fatton, et al., 1993).

Active Mucosal Immunization

The second approach to active immunization is to stimulate the immune defenses of the mucosal linings of the gastrointestinal, respiratory and urogenital tracts, the nasal passages, and the inner ear. These mucosal linings produce immunoglobulin A (IgA). IgA diminishes microbial virulence by preventing microbial adherence to host cells. It also coats the surface of the antigen, making an antigen/IgA complex that stimulates white blood cells to recognize, engulf, and destroy any pathogen expressing that antigen. Mucosal lymphocytes also trigger production of circulating IgG antibodies. Current targets for mucosal immunity include *Helicobacter pylori*, *Clostridium difficile*, *Shigella flexneri*, Campylobacter strains, and certain strains of *Escherichia coli*.

Mucosal vaccines are immunogenic only if they reach specific immune response tissues beyond the stomach, which requires their surviving passage through stomach acid and enzymes. Some researchers are testing synthetic polymers to protect their vaccines. Another strategy is to use liposomes, lipid-containing vesicles made from the same natural materials that compose mammalian cell membranes.

Helicobacter pylori vaccines

The discovery by Marchetti, Arico, Burroni, et al. (1995) that bacteria isolated from humans with ulcers could infect mice and cause disease processes that mimic those seen in humans has spurred progress toward a vaccine against *H. pylori*, the causative organism. Those researchers found that mice were protected from infection after administration of disrupted *H. pylori* bacteria. This finding, characterized as "of extreme practical importance" (Tompkins and Falkow 1995) may lead to a vaccine to protect the 50 percent of the world's population that are currently infected by *H. pylori*. While *H. pylori* is most often associated with gastritis and ulcers in the United States, elsewhere in the world it is also a common cause of stomach cancers.

Campylobacter vaccines

Campylobacter strains have recently emerged as one of the common causes of diarrhea and may cause 2.5 million cases annually in the United States. Treatment is increasingly complicated by antibiotic resistance. In 1994, the U.S. Navy signed a Cooperative Research and Development Agreement (CRADA) with MicroCarb Inc. for clinical trials of a vaccine against Campylobacter.

Passive immunization

Passive immunization involves administering antibodies directed against specific pathogens to individuals who have not developed such antibodies on their own but who are at risk for infection. This may be due to lack of prior exposure to the pathogen, or due to immunosuppression, which renders the individual's immune system unable to produce antibodies. The antibodies are purified from the blood of healthy donors whose antibody levels are raised by active immunization. The most common example of passive immunization is the administration of Hepatitis B virus-specific gamma-globulin to travelers. Researchers are currently focusing efforts to develop antibodies against *Staph. aureus* and *P. aeruginosa*, both of which are often antibiotic resistant, as well as against other bacteria.

Passive immunization does not always work. Low birthweight babies are at high risk of nosocomial infections because of long hospitalizations and immature immune systems. Injections of pooled human antibodies ("immune globulin") into very low birthweight babies did not reduce the incidence of nosocomial infections compared to the incidence in very low birthweight babies who did not receive the immune globulin (Fanaroff, Korones, Wright, et al., 1994). This failure does not invalidate the idea of passive immunization, even in low birthweight babies, but it underlines the importance of trials of the efficacy of interventions before they are introduced widely into practice.

Vaccine Summary

Vaccines are not high-profit items. UNICEF estimates that the entire global vaccine market is about $3 billion, which can be compared to the $3.5 billion market for a single ulcer drug. While vaccine development against bacteria that have high frequencies of antibiotic-resistant strains, such as *Staph. aureus* or *S. pneumonia*, would reduce infections by those bacteria, few vaccines will be developed for bacteria solely because of the problems raised by antibiotic resistance. Instead, the general problems raised by the bacteria may lead to development of a vaccine that will protect against both antibiotic susceptible and resistant strains.

STIMULATING THE IMMUNE SYSTEM

Granulocyte colony-stimulating factor (G-CSF) is a growth factor that stimulates the proliferation of neutrophil cells, important components of the immune system. Crawford, Ozer, Stoller, et al. (1991) have shown that the administration of G-CSF to cancer patients on chemotherapy led to a 51 percent reduction in culture-confirmed infections, a 47 percent reduction in the mean number of days of antibiotic use, and a 45 percent reduction in the mean number of days of hospitalization. G-CSF in the form of filgrastim (Amgen, Thousand Oaks, California) has been approved by the FDA and is clinically available.

TARGETED DELIVERY OF ANTIBIOTICS

Some sites of infection or potential infection are localized, such as wounds or the area around a joint replacement. Delivery of antibiotics directly to those sites may stop the growth of susceptible bacteria, and if the concentration can be raised high enough, it may even stop the growth of many resistant bacteria. Direct delivery of antibiotics in this way has the additional advantage of producing only very low levels of circulating antibiotics, thus reducing pressure for the selection of resistant bacteria elsewhere in the body.

▮ Microencapsulation

Entry into the body, whether surgical or traumatic, opens pathways for infection. Surgical patients who develop wound infections spent, on average, 14.3 days longer in the hospital than uninfected matched controls (Maderazo, Judson, and Pasternak, 1988), at an increased cost of $36,000 to $45,000 per patient (Cohen, 1994; Daly, Eliopoulos, Reiszner, et al., 1988). Twenty-four percent of United States servicemen who sustained open fracture wounds in Panama during Operation "Just Cause" developed wound infections (Jacob, Erpelding, and Murphy, 1992), and 48 percent of wounded United States soldiers in the Persian Gulf conflict who sustained open fractures developed postoperative infections (Travis and Cosio, 1993). Gustilo, Mendoza, and Williams (1984) report similar infection rates in civilians with severe open fractures of the tibia. Many of these infections occur in patients who receive very large doses of systemic antibiotics.

Researchers at the Walter Reed Army Institute of Research (WRAIR) have developed a novel biodegradable local antibiotic delivery system that promises to decrease infections in wounds. They encapsulate an antibiotic in a copolymer of poly (DL-lactide-coglycolide) to produce microspheres 50 to 250 micrometers (μm) in diameter. Dusted into wounds after surgery, these microspheres provide an initial burst of the antibiotic within the first few hours and prolonged drug release over a period of up to 21 days. After 2 to 3 months, the microspheres completely degrade. As of March 1995, the WRAIR researchers had constructed microspheres containing ampicillin, cefazolin, cefamandole, and tobramycin.

Cefazolin-containing microspheres were used to treat wounds in rats that had been intentionally infected with cefazolin-resistant MRSA, and they were as effective as free cefazolin powder in eliminating MRSA. Systemic administration of cefazolin, on the other hand, had no effect on the MRSA infections. In a similar experiment involving ampicillin-resistant MRSA, microspheres containing ampicillin were more effec-

tive than free ampicillin powder, and systemic ampicillin had no effect.

The United States Army, which developed this technique (Setterstrom, Tice, and Myers, 1994; Jacob, Setterstrom, Bach, et al., 1991; Jacob, Cierny, Fallon, et al., 1993), has a patent pending on it. Further development will require private funding to take the research from the preclinical stage to trials in humans.

Antibiotic-Impregnated Cement

Bone infections and infections of joint prostheses are hard to treat with systemic antibiotics, partially because limited blood flow to the skeletal tissues does not allow high concentrations of the drug to reach the area of infection. An antibiotic-impregnated polymer, poly (methyl-methacrylate) (PMMA), has been used to cement bone fractures and prostheses in place, and has shown clinical success, but its usefulness is limited by the toxicity of the material and shrinkage which leaves marginal mechanical support for the remaining bone. Yu, et al. (1992) described hydroxyapatite (HAP) cement, which has the same chemical composition as bone mineral. This material can be molded to fill the space left by the absence of bone, and Yu, et al. demonstrated that antibiotics impregnated in this material are slowly released. They concluded that this material is very promising for preventing infections in bone fractures and in joining prostheses, and they propose future in vivo experiments.

Biological Substances to Facilitate the Entry of Antibiotics into Bacteria

One mechanism of resistance involves bacterial cell walls in excluding antibiotics from the bacterial cell. Research is underway on biological substances that allow antibiotics to penetrate into such bacteria. For example, because iron is insoluble but necessary for bacterial metabolism, bacteria synthesize and excrete compounds that can bind iron ions, called "siderophores." These compounds scavenge iron outside the cell, and the cell then transports the iron-siderophore compound back inside the cell. Inside the cell, the iron-siderophore complex is metabolized by the bacteria, releasing iron for bacterial use. Siderophores may be modified to carry antibiotics into the bacteria. These may be especially useful in the treatment of Gram-negative bacterial infections. Although the outer cell membrane channels ("porins") of Gram-negative bacteria are too small to accommodate many antibiotics, siderophores enter the cell via a non-porin route, and researchers reason that antibiotics attached to siderophores might be "dragged" inside.

Over 200 siderophore molecular structures are known. Often, only portions of the siderophores are required to penetrate the cell. One goal of current research is to optimize synthetic siderophores in order to make their transport into bacterial cells more efficient. Synthetic siderophores, when conjugated with beta-lactam antibiotics or erythromycin, can carry the antibiotic across bacterial cell membranes with high efficiency. These antibiotics kill bacteria when delivered inside the cell in this manner (Miller, 1989; McKee, Sharma, and Miller, 1991). Siderophores are also being explored for their potential to transport vancomycins. Although siderophore/antibiotic conjugates have thus far been used only as antibacterials, researchers are currently attempting to apply the same methodology to antifungal/siderophore conjugates.

REDUCING INFECTIONS BY MODIFYING DEVICES

Several hundred thousand cases of hospital acquired infection per year are related to the use of medical devices such as catheters, endotracheal tubes and mechanical ventilators (IOM, 1992). These devices provide extra opportunities for bacteria to enter the body. Experience with dialysis, the filtering of the blood of patients with kidney disease, indicates that changing the design and materials of medical devices can minimize infections.

Infections in Dialysis Patients

In 1991, there were approximately 120,000 patients on maintenance dialysis (Favero, Alter,

and Bland, 1992) with 45,000 new patients added per year. Infections are the cause of death in 15 to 30 percent of dialysis patients.

The technique called hemodialysis is used to treat approximately 85 percent of dialysis patients. Simulating the function normally performed by the kidney, it filters the patient's blood through a membrane which separates out unwanted components and adds needed components. Cupraphane membranes, the most commonly used filtration membrane in hemodialysis, are made from cotton fibers dissolved in an ammonia solution of cupric oxide. Recently, membranes made of synthetic polymers such as polysulfone (PS), polymethylmethacrylate (PMMA) and polyacrylonitirile (PAN) have been developed. A recent review of the properties of hemodialysis membrane (Hakim, 1993) describes how the interaction of blood with cotton fiber membranes such as Cupraphane produces a decrease in the immune functions in the blood, leaving the patient more susceptible to infection. The membranes made of synthetic polymers do not seem to decrease the immune functions in the blood. Retrospective studies showed that replacing a Cupraphane membrane with a polysulfone membrane eliminated 50 percent of the infections.

Another 15 percent of patients are on peritoneal dialysis. In this technique, fluid is pumped into the patient's abdomen, allowing exchange of blood components through the peritoneal lining of the abdomen. A recent review (Diaz-Buxo, 1993) shows that the incidence of peritonitis (peritoneal infection) was twice as high when older CAPD (continuous ambulatory peritoneal dialysis) machines were used than when new dialysis machines of different design, such as CCPD (continuous cyclic peritoneal dialysis) machines and Y-set connections for CAPD, were used. This may be because the order of flow is reversed in CCPD and Y-set CAPD compared to other forms of CAPD, so that the connections (and contaminating bacteria) are washed out before fluid is pumped into the body. Diaz-Buxo comments that CAPD machines are more common than CCPD machines, partially because of the lower cost of the machine itself. When the total costs of the two systems were calculated, including the cost of the machine and the cost of hospitalization for peritoneal infections, the total costs were the same (King, et al., 1992).

Analyzing the costs of dialysis for kidney patients is especially interesting because dialysis patients have been covered by Medicare since 1973 regardless of their age. Medicare pays a set amount per patient for dialysis and pays separately for any hospitalization necessitated by complications. Under this system, physicians have a financial incentive to use the least expensive equipment. However, it would be beneficial to the patients, and probably cheaper for Medicare, to use the more expensive equipment and prevent infections that may require hospitalization. Outpatient costs, primarily dialysis, accounted for 33 percent of total costs compared with 44 percent of total costs attributable to hospitalizations (Smits, 1995). (The remainder of the costs were for physician services, skilled nursing care, and home health care.) This demonstrates that investing in new technologies that prevent infections and hospitalizations can be cost-effective. These investments would also reduce antibiotic resistance by preventing infections and thus reducing the use of antibiotics.

Infections from Sutures and Catheters

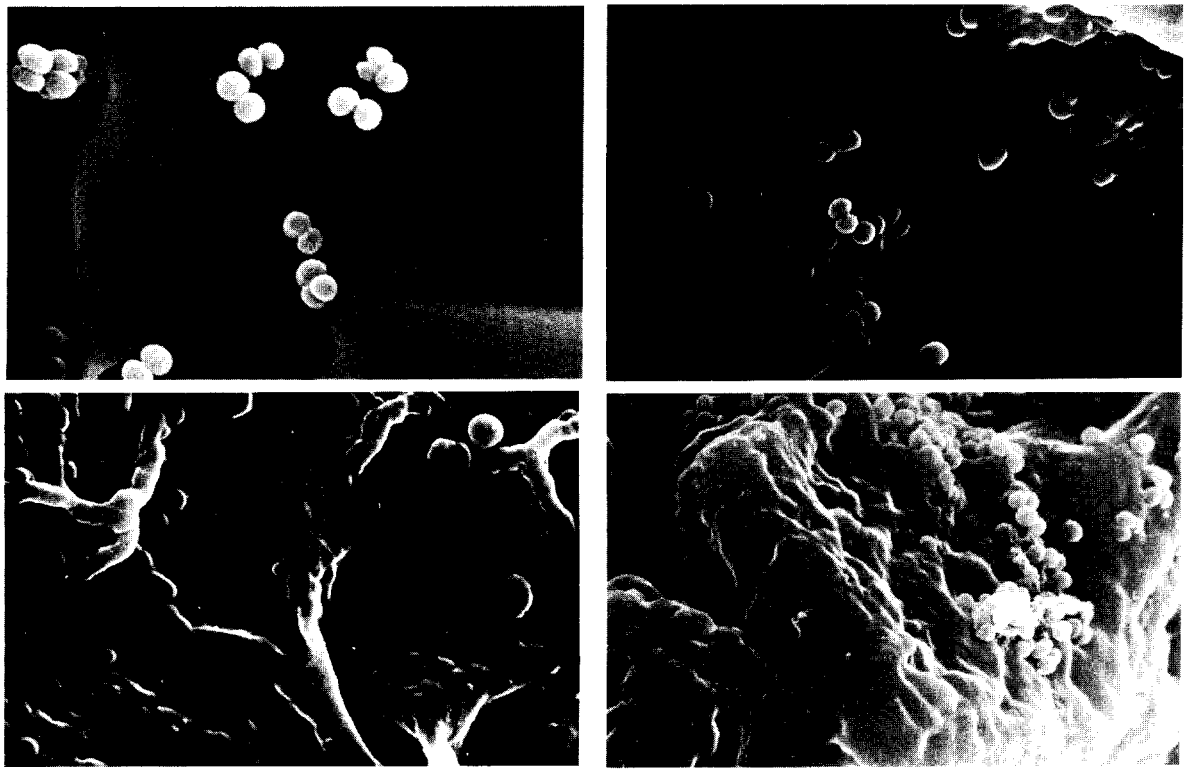
Improvements in the materials used for other medical devices such as sutures and catheters could also greatly reduce the rate of infection. In particular, sutures made of synthetic materials such as dacron and nylon have lower infection rates compared to natural sutures such as cotton, silk and catgut, and monofilament sutures have lower infection rates compared to polyfilament sutures.

Studies of the colonization of medical devices by coagulase-negative staphylococci (Christensen, Baldassarri, and Simpson, 1994) provides some insight into why some suture materials are associated with infections more than others. The process of colonization of non-biological surfaces by coagulase-negative staphylococci is

shown in the photograph. The first step in colonization is binding and/or trapping a "unique site" on the surface, such as a microscopic crack or depression in the surface of the material. Synthetic materials such as nylon and plastics are generally much smoother than natural materials such as cotton and silk and therefore have fewer unique sites. Similarly, monofilament are smoother than polyfilaments. Therefore, it is not surprising that the natural materials and polyfilaments are more often associated with infections than the synthetic materials and monofilaments. Knowledge about the colonization and infection process for non-biological materials will help guide new designs of medical devices that may minimize infections and reduce the need for antibiotics.

Maki (1 994) reviewed innovative designs that help prevent infections in intravascular catheters used for infusion therapy. Some catheters have a new design that creates mechanical barriers against infection at the entrance of the catheter to the skin. Other designs create a closed system; for example, they replace the stopcocks used to obtain blood specimens from arterial lines with a diaphragm. Such closed systems reduce the rate of infection.

Another strategy for preventing infections is to coat the materials used in medical devices with antibiotics or other antibacterial agents. Like the microencapsulated antibiotics and antibiotic-impregnated cement, these coated catheters may have the advantage of delivering high concentrations of antibiotics to the site of potential infection with much lower systemic antibiotic concentrations. In one system, the catheters are coated or impregnated with silver ions, which are bactericidal but non-toxic to humans. (Manufacturers include Arrow International and C.R. Bard Urological Division; Maki, et al., 1991; Stamm, 1991). In another system, catheters are coated with materials bearing positively charged chemicals, to which negatively charged antibiot-



Series of four microphotograph demonstrating the colonization of a non-biological surface. Courtesy of Meryl E. Olson, University of Calgary, Calgary, Canada

ics are bound (Cook Bio-Guard AB coated catheters, Cook Critical Care). A trial with these catheters coated with cefazolin showed a sevenfold decrease in the infection rate (Kamal, Pfaller, Rempe, et al., 1991). Further, a reduction in the infection rate was seen even if the catheters were changed only once every seven days (compared to once every four days for standard catheters; Kamal, Divishek, Adams, et al., 1994). The longer life of the coated catheter compensates for its higher cost (about $4.50 more per catheter).

OLD THERAPIES

In the pre-antibiotic era, scientists and physicians tried different methods to treat bacterial infections. Two of those methods, "phage therapy" and "serum therapy," are now mentioned as possible treatments in a post-antibiotic era.

Phage Therapy

While most people may not recognize the term "phage therapy," many people read about it in *Arrowsmith*. The hero of that novel tried to treat bacterial infections by the use of viruses that would specifically attack the bacteria, and in real life, many physicians tried the same method in the early part of this century. Because viruses that infect bacteria are called "bacteriophages" (literally, eaters of bacteria) or "phages" for short, the treatment is called "phage therapy." Phage therapy has remained outside the mainstream of medicine because of doubts about its efficacy and the success of antibiotics.

Phages recognize specific binding sites on the bacteria. Therefore, phages that infect *E. coli* generally do not infect other bacteria, and, in fact, sometimes will only recognize a single strain of bacteria. This specificity offers the promise of being able to prepare phages to attack particular bacteria.

Levin and Bull (1995) and Levin, DeRouin, Moore, et al. (1995) review the literature about phage therapy. They focus on some recent experiments with systems that involve mice infected with *E. coli* and argue that phage therapy is worth renewed investigation. While they do not think that it will replace antibiotics, they believe that it may have some future use in treating antibiotic-resistant bacteria. They also argue that the time to develop alternatives to antibiotic therapy is now, when antibiotics remain effective against most diseases.

Serum Therapy

Textbooks of medicine and of microbiology published before 1940 are filled with instructions for serum therapy. In some respects similar to passive immunization, serum therapy involves taking blood serum from horses or rabbits that have survived an intentional bacterial infection and injecting it into a patient suffering from an infection by the same organism.

Serum is still used in the treatment of some diseases that involve bacterial toxins; in particular, tetanus and botulism are treated with horse serum. Serum for the treatment of botulism is kept at several major airports around the country, ready for shipment to hospitals that diagnose the rare disease. (According to the CDC [1979], there were about 10 outbreaks of botulism, involving about 2.5 people per outbreak, each year in the period 1899 through 1977.) For other infections, serum therapy was replaced as antibiotics became available. A patient's possible anaphylactic response to chemical substances in the animal serum is the chief danger.

Serum therapy may have application in treating *Escherichia coli* O157:H7, which became famous as the cause of more than 500 cases of disease and perhaps four deaths in people who ate under-cooked fast-food hamburgers in the Pacific Northwest in early 1993. The usual treatment for the disease does not include antibiotics (Salyers and Whitt, 1994). Antibiotics have not been shown to shorten the course of the disease or to reduce the occurrence of kidney complication. Further, antibiotic treatment may cause the bacteria to increase the production of the bacterial toxin that causes the disease. The cause of disease in *E. coli* O157:H7 infections is a toxin that resembles the Shigella toxin that causes dys-

entery. That toxin has been isolated and purified. Antibodies generated against the toxin have potential in treating *E. coli* O157:H7-caused diseases, but the market for such a drug is small, and no trials are in progress.

SUMMARY

This chapter reviews some new technologies that will help health care providers use antibiotics more effectively. Diagnostic technologies help the clinician identify the specific bacteria causing the infection and its susceptibility to antibiotics. This information is critical for choosing the most appropriate antibiotic. New technologies, such as DNA identification of antibiotic resistance genes, have the potential to provide this information more quickly than is possible with traditional diagnostic tests, which require growing the bacteria in cultures. These new diagnostic technologies have already proven useful in diagnosing tuberculosis. Many companies are rapidly developing additional tests for TB and other bacteria. There are unresolved issues with respect to the accuracy, sensitivity, and reproducibility of these tests. These issues may not be resolved until the tests have received FDA review and are widely used in clinical settings. This chapter discusses some of these issues.

Preventing infections is another way to slow the increase of antibiotic-resistant bacteria because prevention will reduce the total use of antibiotics. Methods of preventing infection include vaccines and changes in the design and composition of medical devices to prevent the growth of bacteria. The recent introduction of a vaccine against *Hemophilus influenza B* resulted in a dramatic reduction in the incidence of childhood diseases caused by this bacteria. A number of other vaccines are under development, including those for *Staphylococcus aureus*, as well as better vaccines for *Streptococcus pneumoniae*. Indwelling devices and sutures are often ports of entry for bacteria into the body, and improved devices and materials have been shown to reduce infection rates. Further research and application could produce further reductions.

REFERENCES

Abe, C., K. Hirano, M. Wada, et al. 1993. Detection of *Mycobacterium tuberculosis* in clinical specimens by polymerase chain reaction and Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. *Journal of Clinical Microbiology 31:*3270–3274.

Adams, W.G., K.A. Deaver, S.L. Cochi, et al. 1993. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *Journal of the American Medical Association 269:*221–226.

American Medical News. March 27, 1995. Chicago, IL. American Medical Association.

Bellin, E. 1994. Letter to the Editor. *Journal of the American Medical Association 272:* 765.

Christensen, G.D., L. Baldassarri, and W.A. Simpson. 1994. Colonization of medical devices by coagulase-negative staphylococci. In: A.L. Bisno and F.A. Waldvogel (eds.) *Infections Associated with Indwelling Medical Devices*. Washington, DC. ASM Press.

Cohen, M.L. 1994. Antibiotic resistance: Prognosis for public health. *Trends in Microbiology 2:*422–425.

Coldwitz, G.A., T.F. Brewer, C.S. Berkey, et al. 1994. Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. *Journal of the American Medical Association 271:*698–702.

Coldwitz, G.A., T.F. Brewer, C.S. Berkey, et al. 1994a. Letter to the Editor. *Journal of the American Medical Association 272:*766.

Comstock, G. 1994. Letter to the Editor. *Journal of the American Medical Association 272:*766.

Crawford, J., H. Ozer, R. Stoller, et al. 1991. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *New England Journal of Medicine 325:*164–170.

Daly, J.S., G.M. Eliopoulos, E. Reiszner, et al. 1988. Activity and mechanism of action of DuP105 and DuP721, new oxazolidonone compounds. *Journal Antimicrobial Chemotherapy 21:*721–730.

Diaz-Buxo, J.A. 1993. Differences between CAPD and CCPD: Implications for therapy. *Seminars in Dialysis 6:*312–315.

Doern, G.V., D.R. Scott, and A.L. Rashad. 1982. Clinical impact of rapid antimicrobial susceptibility testing of blood culture isolates. *Antimicrobial Agents and Chemotherapy 21:*1023–1024.

Doern, G.V., R. Vautour, M. Gaudet, et al. 1994. Clinical impact of rapid in-vitro susceptibility testing and bacterial identification. *Journal of Clinical Microbiology 32:*1757–1762.

Edwards, L.D., S. Levin, R. Balogtas, et al. 1973. Ordering patterns and utilization of bacteriologic identification. *Archives of Internal Medicine 132:*678–682.

Fanaroff, A.A., S.B. Korones, L.L. Wright, et al. 1994. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. *New England Journal of Medicine 330*:1107–1113.

Fatton, A., R. Schneerson, S.C. Szu, et al. 1990. Synthesis and immunologic properties in mice of vaccine composed of *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides conjugated to *Pseudomonas aeruginosa* exotoxin A. *Infection and Immunity 58*:2367–2374.

Fatton, A., J. Shiloach, D. Bryla, et al. Comparative immunogenicity of conjugates composed of the *Staphylococcus aureus* type 8 capsular polysaccharide bound to carrier proteins by adipic acid dihydrazide or N-succinimidyl-3(2-pyridyldithio) propionate. *Infection and Immunity 60*:584–589.

Favero, M.S., M.J. Alter, and L.A. Bland. 1992. Dialysis-associated infections and their control. In: J.V. Bennett, and P.S. Brachman (eds.) *Hospital Infections Third Edition.* Boston, MA. Little, Brown and Company.

Gustilo, R.B., R.M. Mendoza, and D.N. Williams. 1984. Problems in the management of type III (severe) open fractures: A new classification of type III open fractures. *Journal of Trauma 24:*742–746.

Haas, D.W., and R.M. Des Prez. 1995. Mycobacterium tuberculosis. In: G.L. Mandell, J.E. Bennett, and R. Dolin (eds.) *Mandel, Douglas and Bennett's Principles and Practice of Infectious Diseases Fourth edition.* New York, NY. Churchill Livingstone, Inc.

Hakin, R.M. 1993. Clinical implications of hemodialysis membrane biocompatibility. *Kidney International 44:*484–494.

Hewlette, D. Jr., D.L. Horn, and C. Alfalla. 1995. Drug-resistant tuberculosis: Inconsistent results of pyrazinamide susceptibility testing. *Journal of the American Medical Association 273:*916–917.

Heiter, B.J., and B.P. Bourbeau. 1993. Comparison of the Gen-Probe Group A Streptococcus Direct Test with culture and rapid streptococcal antigen detection assay for diagnosis of streptococcal pharyngitis. *Journal of Clinical Microbiology 31*(8):2070–2073.

Institute of Medicine. 1992. *Emerging Infectious Diseases.* Washington, DC. National Academy Press.

Jacob, E., G. Cierny, M.T. Fallon, et al. 1993. Evaluation of biodegradable cefazolin sodium microspheres for the prevention of infections in rabbits with experimental opent tibial fractures stabilized with internal fixation. *Journal of Orthopedic Research 11:*404–411.

Jacob, E., J.M. Erpelding, and K.P. Murphy. 1992. A retrospective analysis of open fractures sustained by U.S. military personnel during Operation Just Cause. *Military Medicine 157:*552–556.

Jacob, E., J.A. Setterstrom, D.E. Bach, et al. 1991. Evaluation of biodegradable ampicillin anhydrate microcapsules for local treatment of experimental staphylococcal osteromyelitis. *Clinical Orthopedics 267:*237–244.

Jacobs, W.R., Jr., R.G. Barletta, R. Udani, et al. 1993. Rapid assessment of drug susceptibilities of *Mycobacterium tuberculosis* by means of luciferase reporter phages. *Science 260:*819–822)

Jorgensen, J.H. 1993. Recent developments in automated and rapid susceptibility testing methods. In: R.C. Spencer, E.P. Wright, and

S.W.B. Newson (eds.) *Rapid Methods and Automation in Microbiology and Immunology*. Andover, England. Intercept Ltd.

Jorgensen, J.H. 1995. Current and Future Phenotypic Methods for Detection of Resistant Bacteria. Contract report to the Office of Technology Assessment. Photocopied typescript.

Jorgensen, J.H., and J.M. Matsen. 1987. Physician acceptance and application of rapid microbiology instrument test results. In: J.H. Jorgensen (ed.) *Automation in Clinical Microbiology*. Boca Raton, FL. CRC Press, Inc.

Kamal, G., D. Divishek, J. Adams, et al. 1994. Reduced intravascular catheter infection by routine use of antibiotic bonded catheters (abstract). *Critical Care Medicine 22:*A115.

Kamal, G.D., M.A. Pfaller, L.E. Rempe, et al. 1991. Reduced intravascular catheter infection by antibiotic bonding: A prospective, randomized, controlled trial. *Journal of the American Medical Association 265:*2364–2368.

King, L.K., J.C. Kingswood, P. Sharpstone. 1992. Comparison of the efficacy, cost, and complication rate of APD and CAPD as long-term outpatient treatments for renal failure. In: R. Khanna, K.D. Nolph, B.F. Prowant, et al. (eds.) *Advances in Peritoneal Dialysis. Vol. 8.* Toronto, Canada. pp. 123–126.

Kohner, P., C. Kolbert, D. Geha, et al. 1994. Evaluation of the BBL Crystal MRSA ID System for the detection of methicillin resistance in Staphylococci. Abstract presented at the 93rd General Meeting, American Society for Microbiology, Las Vegas, Nevada.

Kuusela, P., P. Hilden, K. Savolainen, et al. 1994. Rapid detection of methicillin-resistant *Staphylococcus aureus* strains not identified by slide agglutination tests. *Journal of Clinical Microbiology 32:*143–147.

Levin, B.R. and J.J. Bull. 1995. Phage therapy revisited: The population biology of a bacterial infection and its treatment with bacteriophage and antibiotics. *American Naturalist.* Submitted.

Levin, B.R., T. DeRouin, N. Moore, and J.J. Bull. 1995. Phage therapy revisited II: An experimental study of the population dynamics of a bacterial infection and its control with antibiotics and bacteriophage. *Microbiology.* Submitted.

Macher, A. and E. Goosby. 1995. PCR and the misdiagnosis of active tuberculosis. Letter. *New England Journal of Medicine 332*(2):128–129.

Maderazo, E.G., S. Judson, and H. Pasternak. 1988. Late infections of total joint prosthesis. *Clinical Orthopedics 229:*131–142.

Maki, D.G. 1994. Infections caused by intravascular devices used for infusion therapy: pathogenesis, prevention, and management. In: A.L. Bisno and F.A. Waldvogel (eds.) *Infections Associated with Indwelling Medical Devices.* Washington, DC. ASM Press.

Marchetti, M., B. Arico, D. Burroni, et al. 1995. Development of a mouse model of *Helicobacter pylori* infection that mimics human disease. *Science 267:*1655–1658.

McKee, J.A., S.K. Sharma, and M.J. Miller. 1991. Iron transport mediated drug delivery systems: Synthesis and antibacterial activity of spermidine- and lysine-based siderophore-β lactam conjugates. *Bioconjugate Chemistry 2:*281–291.

Miller, M.J. 1989. Synthesis and therapeutic potential of hydroxamic acid based siderophores and analogues. *Chemical Reviews 89:*1563–1579.

Medical World News. 1995. CDC says many elderly skipping pneumovax. *Medical World News 34*(6):11.

O'Brien, T. 1994. Remarks at U.S. Food and Drug Administration, Part 15 Hearing: Surveillance Systems for Antibacterial Resistance. Rockville, MD, November 9, 1994.

Rippin, K., C. Carlyn, J. Goldfard, et al. 1994. Rapid direct DNA probe testing of throat swabs for group A Streptocccus (GrAS) from pediatric patients. Abstract D1. *Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Washington, DC. American Society for Microbiology.

Salyers, A.A. and D.D. Whitt. 1994. *Bacterial Pathogenesis: A Molecular Approach.* Washington, DC. ASM Press.

Setterstrom, J.A., T.R. Tice, and W.E. Myers. 1984. Development of encapsulated antibiotics for topical administration to wound. In: J.M. Anderson, and S.W. Kim (eds.) 1984. *Recent Advances in Drug Delivery Systems.* New York, NY. Plenum Press, pp. 185–198.

Siber, G.R. 1994. Pneumococcal disease: prospects for a new generation of vaccines. *Science 265:*1385–1387.

Smits, H. 1995. Testimony presented before the Subcommittee on Health, Committee on Ways and Means, United States House of Representatives, on the Medicare End Stage Renal Disease (Kidney Failure) Program, April 3.

Stamm, W.E. 1991. Catheter-associated urinary tract infections: epidemiology, pathogenesis, and prevention. *American Journal of Medicine 91*(3B):65S–71S.

Stratton, C.W., and R.C. Cooksey. 1990. Susceptibility tests: special tests. In: A. Balows, W.J. Hausler, K.L. Herrmann, et al. *Manual of Clinical Microbiology, 5th Edition.* Washington, DC. American Society of Microbiology.

Tompkins, L.S., and S. Falkow. 1995. The new path to preventing ulcers. *Science 267:*1621–1622.

Travis, M.T., and M.Q. Cosio. 1993. A retrospective review of orthopedic patients returning from Operation Desert Shield and Desert Storm to an Army medical center. *Military Medicine 158:*348–351.

Trenholme, G.M., R.L. Kaplan, P.H. Karahusis, et al. 1989. Clinical impact of rapid identification and susceptibility testing of bacterial blood culture isolates. *Journal of Clinical Microbiology 27:*1342–1345.

Univax Biologics, Inc. Rockville, MD. 1994. Personal communication to D. Frankle. Data on file.

U.S. Congress, Office of Technology Assessment. 1993. *The Continuing Challenge of Tuberculosis.* U.S. Government Printing Office: Washington, DC.

U.S. Department of Health and Human Services, Food and Drug Administration. 1995. Comments on second draft of this OTA report. Memorandum from Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration to Office of Technology Assessment. June 16.

U.S. Department of Health, Education, and Welfare, Center for Disease Control. 1979. *Botulism in the United States, 1899–1977. Handbook for Epidemiologists, Clinicians, and Laboratory Workers.* Washington, DC.

Wanger A. and Mills K. 1995. E-Test for Susceptibility Testing of *Mycobacterium tuberculosis* to first line antituberculosis agents. Poster U-67. American Society for Microbiology 95th General Meeting. Washington DC.

Weinstein, M.P., J.R. Murphy, L.B. Reller, et al. 1983. The clinical significance of positive blood cultures: A comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special references to factors influencing prognosis. *Reviews of Infectious Disease 5:*54–70.

Wenger, J.D. 1994. Mini review: Impact of *Haemophilus influenzae* type B vaccines on the epidemiology of bacterial meningitis. *Infectious Agents and Disease 2:*324–332.

Wheeler, J.G., L.C. Rodrigues, and V. Diwan. 1994. Letter to the Editor. *Journal of the American Medical Association 272:*765–766.

Wischnack, L.L., R.M. Jacobson, G.A. Poland, et al. 1995. The surprisingly high acceptability of low-efficacy vaccines for otitis media: A survey of parents using hypothetical scenarios. *Pediatrics 95:*350–354.

Yu et al. 1992. Self-setting hydroxyapatite cement: a novel skeletal drug-delivery system for antibiotics. *Journal Pharmaceutical Sciences 81:*529–531.

Antibiotics in Animal Husbandry 7

What effect does the use of antibiotics in food production have on the occurrence of antibiotic-resistant bacteria? Everyone concerned with that question agrees about a few things: About half of the antibiotics (by weight) used in the United States are used in the production of food animals, much smaller amounts are used to control bacterial diseases in plants and in fish farming, and some proportion of the bacteria that are present in and on food may survive cooking or other preparation in the food eaten by humans. Beyond such small areas of agreement, there is widespread disagreement, or so it would seem. In fact, the real questions about the transfer of antibiotic-resistant bacteria from foods to humans are how often does it happen and what are its consequences, rather than does it happen at all.

The chairman of a National Research Council (NRC) advisory panel that looked at the question neatly posed a scenario for the risks from use of antibiotics in farm animals:

> ...a beef producer feeds tetracycline in low doses to his calves to encourage rapid weight gain; nonpathogenic *Escherichia coli* in the guts of the calves acquire antibiotic resistance. Somewhere along the chain from feedlot to dinner table, the *E. coli* may come into close association with some salmonella, and the salmonella may acquire resistance to antibiotics by plasmid transfer. The meat eater becomes infected, develops *Salmonella* septicemia and dies while his physicians are treating him with an inadequate antibiotic (Stallones, 1982).

The scenario is clearly stated, but how often does it occur? That question could be answered by identifying people who harbor antibiotic-resistant bacteria and linking those bacteria to meat that was derived from antibiotic-treated animals. That has proved impossible to do; there are many possible sources for bacteria, each one would have to be eliminated, and it is difficult to trace the origins of "meat" as it arrives at a butcher shop or supermarket. "[S]ome studies can be conceived but cannot be delivered" (Stallones, 1982).

In the absence of definitive information, disagreements about the significance of antibiotic use in agriculture on the emergence of antibiotic-resistant human pathogens have fostered several reviews and analyses of the data about animal to human transfer of antibiotic-resistant bacteria. Congress requested an Office of Technology Assessment (OTA) study, *Drugs in Livestock Feed*, that reviewed risks and benefits of antibiotic (and other drug) use in agriculture including

the risks of increasing the prevalence of antibiotic-resistant bacteria in humans (OTA 1979). OTA did not reach a hard and fast conclusion about the magnitude of the risk. Instead, it put that risk in context by comparing it to the risk of antibiotic resistance developing as a result of antibiotic use in medicine, and concluded that the risk exists, but that it is less than the risk from uses of antibiotics in humans:

> The risk from resistant plasmids of animal origin is not quantifiable....The majority of resistance in human bacterial populations is probably caused by widespread use of antibacterials in humans (some of which are unnecessary), but the enormous pool of R-plasmids that now exist in animals, together with the ability of an R-plasmid to be promiscuously transferred among bacterial species, must be regarded as a threat to the therapeutic value of antibacterials in the treatment of both human and animal diseases. (U.S. Congress, Office of Technology Assessment 1979, p. 7)

A year later, an NRC committee (1980) reached a similar conclusion, and painted a bleak picture about the possibility of learning more:

> After reviewing the evidence, the committee concluded that the postulations concerning the hazards to human health that might result from the addition of subtherapeutic antimicrobials to foods have been neither proven nor disproven. The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk has not been conducted, and, indeed may not be possible.

In contrast to the report's conclusion that suggests the possibility of a link between uses of antibiotics in animals and human health, the chairman of the NRC committee, in a later publication, downplayed any risk: "If the decision were mine, the hog farmers could use all the antibiotic drugs they wish to make the pigs grow. The risk to humans looks to me to be vanishingly small" (Stallones, 1982). Not everyone shared that opinion, and studies and reviews have continued to the present time.

Almost a decade later, the Institute of Medicine (IOM) issued a report that dealt with the risks from subtherapeutic use of two common antibiotics—penicillin and two kinds of tetracyclines (oxytetracycline and chlortetracycline)—in animal feeds (IOM, 1989). Its authors further narrowed the focus of the report to the risks of antibiotic-resistant Salmonella from animal sources causing human deaths. The authors calculated that,

> "The likeliest estimate of excess deaths attributable to subtherapeutic uses of penicillin and/or the tetracylines...is in the range of 6 per year."

The committee also considered the difficulties that might arise in treating antibiotic-resistant Salmonella infections in humans and calculated that,

> "The likeliest estimate of deaths...arising because of 'increased difficulty of disease treatment' is 20 per year."

At the same time, the committee acknowledged that it

> "was unable to find a substantial body of *direct* evidence that established the existence of a definite human health hazard in the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feeds."

The controversy over the health effects of antibiotic use in animal husbandy has spawned several expert committee reviews that have clarified the issue somewhat (see table 7-1 for a listing of review bodies other than the three mentioned above). There is no doubt that risk exists. There is also no doubt that direct evidence, in the form of studies that show a direct connection between agricultural use of antibiotics and human illness or death, is sparse and difficult to obtain. Moreover, if the IOM committee's estimate of the number of deaths caused by antibiotic-resistant Salmonella of agricultural origin is in the right range, determining what proportion of the 40,000 cases of reported Salmonella infection each year is related to agricultural use of antibiotics is probably impossible.

TABLE 7–1: Reviews—Antibiotics in Animal Feeds

1968	Netherthorpe Committee.
1969	British Government Joint Committee ("Swann Report").[a]
1970–1977	FDA makes several reviews of antibiotic use in animal feeds.
1977	FDA directs its Center for Veterinary Medicine to prepare notice of withdrawal of penicillin and tetracyclines from subtherapeutic uses.
	FDA publishes proposals to restrict subtherapeutic uses. Proposals criticized because of reported inadequate evidence for adverse effects from such uses.
1978	Congressional request to the National Academy of Sciences (NAS) for a study by the National Research Council (NRC) of the effects of subtherapeutic uses.
	FDA Draft Environmental Impact Statement on the Banning of Penicillin and Tetracycline from Animals Feeds.[b]
1979	OTA Report on Drugs in Livestock Feed.[c]
1980	NRC[d] reports that data neither prove nor disprove human health effects from subtherapeutic uses.
1981	House Appropriations Committee provides funds to FDA to study antibiotic in feed issue.
1984	FDA-sponsored study completed. No regulatory action taken.
	The Natural Resources Defense Council (NRDC) petitions the Secretary for Health and Human Services (HHS) for suspension of subtherapeutic uses because such uses pose an "imminent hazard."
	House Committee on Science and Technology holds hearings on the NRDC petition and results of FDA-sponsored study.
	FDA Commissioner holds hearings on same subjects.
1985	Secretary of HHS denies NRDC petition.
1987	FDA makes request to the NAS for a quantitative assessment of the risks from subtherapeutic uses. NAS assigns study to the Institute of Medicine (IOM)
1989	IOM[e] concludes that there is no definitive evidence of adverse effects although such effects may exist.
	Council for Agricultural Science and Technology (CAST) report.[f]
1994	FDA review of fluoroquinolone use.

[a] A subcommittee of the Netherthorpe Committee. Its recommendation results in the United Kingdom forbidding the agricultural use of antibiotics used in human medicine.
[b] Feinman, S.E. and J.C. Matheson, 1978.
[c] OTA, 1979.
[d] National Research Council, 1980.
[e] Institute of Medicine, 1989.
[f] Hays and Black, 1989.

SOURCE: Adapted from U.S. Food and Drug Administration. 1993. *Information for Consumers: Antibiotics in Animals Feeds.* Photocopied typescript and other sources.

Levy (1992, pp. 136–157) summarizes studies that show that bacteria are transferred from farm animals to farm workers, as well as a few studies that show transfer of bacteria to the human community beyond the farm. These studies, however, leave unanswered questions about the quantitative importance of such transfer in the spread of antibiotic-resistant bacteria and, especially, how important such transfer is in comparison to medical use (and overuse) of antibiotics.

OTA does not, in this single chapter of a general report about antibiotic-resistant bacteria, attempt to resolve an issue which has persisted for more than two decades. This report does, however, contain a description of antibiotic uses in animal husbandry and some other aspects of agriculture, an update of some research findings since the release of the 1989 IOM study, and a discussion of a current regulatory proceeding

about approving of fluoroquinolone antibiotics for use in food animals.

ANTIBIOTIC USE IN FOOD PRODUCTION

Everyone, whether a city dweller or farmer, knows about antibiotic uses in medicine. Doctors prescribe antibiotics to treat diseases, in advance of certain surgical procedures to prevent infection, and, sometimes, as prophylaxis during dental procedures to prevent infections in people with heart valve abnormalities. In all these cases the administration of the antibiotic is overseen by a physician.

Paralleling physicians' practice in humans, veterinarians use antibiotics to treat infectious diseases in food (and companion) animals.[1] But from there on, things are different on the farm. There are differences in medical and veterinarian diagnostic laboratories, and veterinarian diagnostic laboratories reportedly do not meet the same standards for accuracy and reliability as do medical laboratories (Walker, 1994). Currently, however, practices are changing in veterinary laboratories, and the National Commission for Clinical Laboratory Standards has recently published the first guideline document for detecting antibiotic sensitivity in animal pathogens. Lack of laboratory quality assurance is not, however, the major difference between uses of antibiotics in animals and humans.

The major difference is that about 90 percent of all the antibiotics used in food animals is used in subtherapeutic doses and not for the treatment of sick animals. For instance, in 1985, veterinarians used about 1 million kilograms (about 2.2 million pounds or 1,100 tons) of antibiotics to treat diseases in cattle, swine, and poultry. During the same year, farmers fed about 5 million kilograms of antibiotics to cattle, swine, and poultry for "disease prevention," and another 2 million kilograms for "growth promotion" (table 7-2). The estimated total of all antibiotics used in cattle, swine, and poultry in that year was 8 million kilograms, or 18 million pounds.

"Disease prevention" describes prophylactic actions taken to stave off the spread of a disease. If a poultry producer notices that a few chickens are ill and he suspects that the illness is caused by bacteria, he could add antibiotics to the feed or water in an effort to stop the spread of the disease. These decisions can be made by the poultry producer acting alone without any involvement of a veterinarian.

"Growth promotion" is a little-understood effect from feeding low levels of antibiotics, generally at a rate of 200 grams or less of antibiotic in each ton of feed. How such levels of antibiotics affect growth is not clear; they may ward off undetectable but consequential, minor infections, or they may have other effects.

Both disease prevention and growth promotion are long-term uses, and the U.S. Food and Drug Administration (FDA) uses 14 days as the threshold for long-term use. When a company requests approval for longer-than-14-day use, FDA requires the company to demonstrate that such use will not increase the shedding of Salmonella (through feces) that might infect humans and that it will not increase the number of antibiotic-resistant bacteria that contaminate carcasses. FDA (1995) has stated that submissions of requests for approval of long-term uses of antibiotics are decreasing, being replaced, in part, by requests for approval of somatotropins and other growth-promoting substances. More specifically, R.H. Teske of FDA (1995) has stated that, "It is not likely that FDA will see applications for long-term use of antibiotics that have therapeutic uses."

There is so much overlap between prophylactic uses and doses and growth-promotion uses and doses that the division between the two applications that is shown in table 7-2 must be regarded as uncertain. Furthermore, the estimates

[1] "In fact, it has been said that the definition of a physician is a veterinarian with a limited knowledge that restricts his practice to a single species." (Walker, R. 1994. Remarks at U.S. Food and Drug Administration, Part 15 Hearing: Surveillance Systems for Antibacterial Resistance, Rockville Civic Center, Rockville, MD, November 10.)

TABLE 7–2: Estimated Annual Use of Antibiotics in Livestock, 1985
All Antibiotics (thousands of kilograms)

	Therapeutic Use	Subtherapeutic Use		
		Disease Prevention	Growth Promotion	Total
Cattle	458	1100	340	1898
Swine	250	3578	1391	5219
Poultry	304	580	315	1199
Total	1112	5258	2046	8316

SOURCE: IOM, 1989, p. 75.

of agricultural use shown in table 7-2 are some 30 percent higher than the estimates produced by the Animal Health Institute for the same year (IOM, 1989, p. 74).

The data in table 7-2 are from 1985, and OTA looked for newer data as part of this report. The only source was a commercial firm that requires purchases of data to join a syndicate, and, as a condition of membership in the syndicate, the purchaser is not allowed to publish the data. OTA did not purchase those data, but experts in the Center for Veterinary Medicine of FDA assert that agricultural uses of antibiotics continue to decline (FDA, 1995).

Most of the antibiotics used in subtherapeutic applications were "old" antibiotics, and penicillins and tetracyclines accounted for 84 percent of antibiotics sold for use in animal feeds in 1985. Some other antibiotics are used only in animals and not in human medicine. These uses make the development of resistance to an antibiotic that is currently used in human medicine less likely. They do not, however, guard against the possibility that a drug closely related to one used in animals will be developed for human use. In that case, resistance to the animal drug, if transferred to bacteria that infect humans, might be cross-resistant to the human drug and reduce its efficacy.

There is an example of possible cross resistance in Europe. In the United States vancomycin-resistant Enterococci (VRE) are found largely, if not exclusively, in large hospitals. In Europe, they are also found in the feces of non-hopitalized patients and of healthy persons, as well as in waste waters, farm animals, and some food products. A glycopeptide called "avoparcin," which is chemically related to vancomycin, has been used as a growth promoter in animal feeds in Europe since the mid-1970s. Bates et al. (1994) reported that VRE were present in fecal materials from farm animals on German farms where avoparcin was used and not present on farms that did not use avoparcin, suggesting that use of the growth promoter was selecting for vancomycin-resistance in Enterococci. Moreover, VRE of the species that infect humans were found in poultry sold in retail markets (Bates et al., 1994; Klare et al., 1995).

Acting on reports of VRE in chickens that had been fed avoparcin, Denmark has banned the use of the drug, and it is now petitioning the European Union to ban it also. Sweden banned use of all growth-promoting antibiotics several years ago. To reduce the emergence and spread of VRE, Murray (1995) urges decreasing use of glycopeptides in animal husbandry and restricting vancomycin use to essential applications in medical practice.

ANTIBIOTIC-RESISTANT BACTERIA IN HUMANS

"While the number and types vary from day-to-day, at any moment in time over 40 percent of people have some antibiotic-resistant bacteria in their colon" (Gorbach, 1993). In the vast majority of cases, these antibiotic-resistant bacteria appear to cause no harm, and they usually constitute a minute proportion of the total bacteria in the intestines, probably one antibiotic-resistant

bacterium for every million or billion or more sensitive bacteria.

▮ Antibiotic-Resistant Bacteria in Food

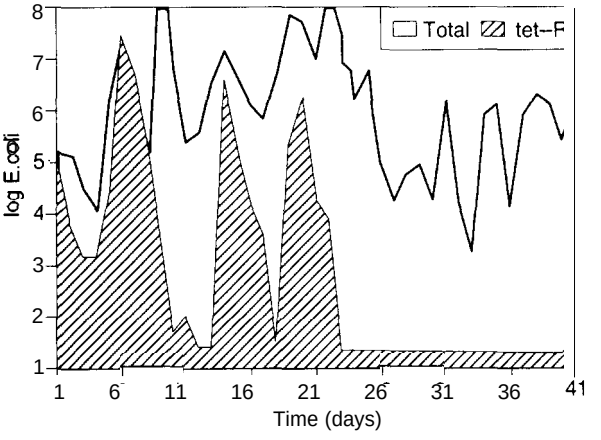
The best evidence is that antibiotic-resistant bacteria are ingested with food every day, that they generally fail to establish themselves in competition against the bacteria already resident in the intestine, and that their numbers fluctuate as a result of the opposing effects of ingestion and elimination. That benign situation can be changed by antibiotics, of course. If a person taking an antibiotic ingests Salmonella that are resistant to that antibiotic, the ingested bacteria will have a growth advantage over the other bacteria. In that case, they may multiply to become a major component of the intestinal flora and cause disease.

Figure 7-1 shows the numbers of tetracycline-sensitive and tetracycline-resistant *Escherichia coli* in feces collected from a volunteer over a 41-day period. During the first 21 days, the volunteer ate a regular diet, and the number of sensitive and resistant bacteria fluctuated daily. For instance, the number of tetracycline-resistant *E. coli* dropped from 107 (10 million) bacteria per gram of stool on day 7 to a low of about $2x10^1$ (20) per gram on day 13. Although the fluctuations in the number of total *E. coli* (susceptible as well as resistant) were not so great, they still varied from about 10^4 (10,000) per gram on day 4 to over 10^8 (100 million) per gram on day 10. These variations are interpreted to reflect, in part, differences in the numbers of *E. coli* ingested daily.

Beginning on day 21, the volunteer ate only sterilized food. The number of tetracycline-resistant *E. coli* dropped to about 20 or less two days later and remained there. The number of tetracycline-sensitive *E. coli* may also have dropped, but not much below the numbers seen on some days when non-sterile food was consumed (days 1 to 8).

Elder et al. (1 993) examined fecal samples from two groups of non-vegetarians and two groups of vegetarians over a 12-month period.

FIGURE 7–1: Tetracyline-resistant and -sensitive *Escherichia coli* bacteria from a volunteer eating non-sterile food (days 1–21) and sterile food (days 21–40).



SOURCE: Corpet, 1993

There were no differences in the prevalence of antibiotic-resistant bacteria in the two groups, and there was a slightly increased frequency of multiply-resistant bacteria in the vegetarians. These results are consistent with the conclusion that meat is not the only source of antibiotic-resistant bacteria, and the authors suggest that restrictions on antibiotic use in animals would have little effect on antibiotic-resistant bacteria in humans. They do not show, however, that meat is unimportant as a source of antibiotic-resistant bacteria, nor do they pinpoint other sources of antibiotic-resistant bacteria in the diet.

Corpet (1993), who carried out the experiment summarized in figure 7-1, concluded that humans' primary source of antibiotic-resistant bacteria is their food, which is consistent with the knowledge that food is a common source of bacterial infections in humans. For instance, Murray (1995) concluded that more than half of Campylobacter infections in humans arise from ingestion of contaminated poultry, and studies of the same organisms, in particular *Campylobacter jejuni* in Washington State, showed that antibiotic resistance patterns were similar in infected humans and in poultry purchased from retail markets (U.S. House of Representatives, 1984).

It is important in this context that both antibiotic-sensitive and antibiotic-resistant *C. jejuni* caused human disease, underlining the importance of other factors in whether or not ingested bacteria will cause illness.

Virulent, antibiotic-resistant Salmonella caused an outbreak of lethal diseases in cattle in England that infected as many as 500 humans and might have contributed to the deaths of 6 individuals (Anderson, 1968). [The closing down of one farm which was in the business of buying and reselling calves apparently stopped that epidemic (Bywater, 1995).] Furthermore, there is no doubt that farmers and others who are around and care for antibiotic-treated livestock can become carriers of bacteria with the same kinds of antibiotic-resistant bacteria as are found in the animals (Levy, 1978, 1983, 1992 and Levy et al., 1976).

Antibiotic-resistant bacteria in food are ingested by humans along with other bacteria, and antibiotic-resistant bacteria can be passed from animals to humans. Questions remain about how often these transmissions cause disease in human beings or promote the flow of genetic information for antibiotic resistance from bacteria of animal origin to bacteria that can cause human disease.

Antibiotic Residues in Food

FDA, in approving uses of an antibiotic in food animals, specifies a "withdrawal period" following the administration of the antibiotic to allow time for the antibiotic "residue" concentration to fall to a level that is of no concern to the agency. When the withdrawal period is observed, and the residue level falls appropriately, the concentration of antibiotics in meat, according to FDA, should have no effect on the bacterial flora in humans. Any meat that has a higher concentration violates the law.

If, however, residue concentrations were high enough, they could have the same effect on humans as ingesting antibiotics directly. Corpet (1993) summarizes a number of experiments that indicate that the concentrations of antibiotics in meats may rarely be sufficient to have an effect on human bacterial flora. He emphasizes, however, that those effects are less important to human health than the ingestion of antibiotic-resistant bacteria.

A number of papers printed in two special issues of journals about veterinary microbiology reached similar conclusions: *Veterinary and Human Toxicology 35* (supplement 1), 1993, and *Veterinary Microbiology 35* (no. 3,4), 1993. Kidd (1994), in a report prepared for the Fédération Européenne de la Santé Animale, comes to a similar conclusion, but cautions that the lack of evidence for any effect of antibiotics in meat may reflect an absence of investigations of the possibility. While there may remain some lingering suspicions that antibiotic residues in meats can affect the micro-organisms in human beings, the remainder of this chapter will focus on the risks of antibiotic-resistant bacteria from food that was treated with antibiotics.

Antibiotics on Plants and Vegetables

Levy (1992, p. 159–167) estimates that 40,000 to 50,000 pounds of antibiotics are used on fruit trees in the United States each year. While that amount is small in comparison to the 18 million pounds of antibiotics used in animals, some of it is sprayed onto fruit trees and other crops, spreading it into the environment, and some of it could be ingested by humans when they consume fruits and vegetables. Oxytetracycline and streptomycin are used to treat various "rots," "molds," and "spots" on fruits and vegetables, and some of the plant pathogens that cause those diseases have developed resistance to the antibiotics. Levy (1992, pp. 163–165) points to the possibility that the bacteria that infect plants serve as a reservoir for antibiotic-resistant genes that can be transferred to other bacteria that infect humans, but this possibility has not been researched.

Antibiotics in Fish

Commercial fish farming is a fast-growing enterprise, and oxytetracycline, a sulfa drug, and a derivative of trimethoprim are used to control

diseases. FDA requires that the antibiotics be withdrawn from the fish for a specified number of days before the fish are sold to reduce transmission of antibiotics to humans, but bacteria can be carried along with the fish when they go to market.

Catfish, raised in ponds, are the primary commercially farmed fish in the United States. Trout are raised in enclosed raceways, and some salmon are raised in ocean netpens in Puget Sound, Washington, and off the Maine coast.

Farmed fish, when treated with antibiotics, are fed medicated feeds. Thus, antibiotics enter the environment either in fish feces or uneaten food. In catfish farming, antibiotics in feces or food drop to the bottom of the pond and are subject to biological binding or degradation in the sediment. When catfish ponds are drained, the sediment is generally placed on the pond levee, restricting movement of the antibiotics into the general environment.

These U.S. practices differ from those elsewhere. In Norway, antibiotics are sometimes sprayed onto the surface of bodies of water and the antibiotic can then spread throughout the water and possibly cause disturbances in the ecosystem. In that country, quinolones, as well as oxytetracycline, are used to treat diseases in farm-grown fish, and Ervik et al. (1994) showed that detectable residues of antibiotics in the flesh of wild fish and mussels in sprayed water bodies were more common than in fish and mussels taken from waters not known to be treated with antibiotics. The frequency of antibiotic-resistant bacteria in fish and mussels near the fish farms was also higher, but the frequency of such bacteria was not zero, even in fish and mussels from untreated waters. This study demonstrates that antibiotics can move through the aquatic environment and affect the flora of wild fish. Its implications for human health are unknown, and not generally applicable to the United States. In particular, no quinolones are approved for use in aquaculture in the United States, and, according to the Animal Health Institute (1995), no such use is contemplated.

CONTROVERSY ABOUT ANTIBIOTIC USE IN RAISING LIVESTOCK

There is little controversy about the desirability of using antibiotics to treat sick animals. More controversy arises about the subtherapeutic uses in prophylaxis and growth promotion, and the possible diversion of antibiotics licensed only for therapeutic purposes to other uses. Whatever the reason for the use of the antibiotic, treatment of animals can result in contamination of meat by antibiotic-resistant bacteria. Three things can happen as a result. The first is that antibiotic-resistant pathogenic bacteria might be transferred to humans. The second is that antibiotic-resistance genes, although present in non-pathogenic bacteria in the animal, may be transferred to pathogenic organisms in humans. The third is that antibiotic-resistant bacteria that do not normally infect humans will be ingested by people on antibiotic therapy, that the therapy will have altered the human flora, and that the alteration will favor the growth of bacteria that pose a risk to human health.

Any of these effects is a risk to human health. Why would anyone subject himself or herself, his or her family, and his or her customers to a risk? Clearly, if there were no apparent gain from using subtherapeutic doses of antibiotics in animals, no one would do it. The manufacturers of antibiotics gain, of course, because such uses increase their sales. But farmers would not be expected to buy the antibiotics if they did not profit from them.

Discussions about subtherapeutic uses have been dominated by concerns about risks, but the fact that the uses continue and are sanctioned by the federal government is convincing evidence of the received benefits. Whatever the risks may be, any decision about subtherapeutic uses will involve considerations of both risks and benefits, and continued focus on efforts to better pin down estimates of risks to the exclusion of benefits may have little effect on the decisions. In any case, as can be seen from the earlier reviews of this issue, determining actual risk is not simple.

How Well Do Subtherapeutic Doses Work?

A measure of the success of subtherapeutic uses of antibiotics in increasing meat production would be provided by information about the amounts of antibiotics that meat producers buy over time. From the limited information available it appears that success varies from animal to animal and from time to time. As discussed below, a major chicken producer uses the same kinds and amounts of subtherapeutic antibiotics as were used years ago, and large-scale pork producers are reducing their use. In addition, small "niche" markets have been developed for meats from drug-free animals, and some producers do not use antibiotics in order to participate in these markets.

While OTA has not carried out any original research or analysis on this issue, it appears that answers to the question of how well subtherapeutic antibiotics work to promote growth depends on the particulars of the application. Unsatisfying as it may be, the answer appears to be, "It depends."

Chickens—Constant Use and Constant Benefits

Chickens are archetypal food animals (see box 7-1). Because of selection for faster growing chickens and attention to animal husbandry, farmers can now produce a 6-pound chicken in 56 days. Thirty years ago, a chicken of the same age weighed two pounds.

Viral infections, against which antibiotics have no effect, are a far greater threat to chickens than are bacterial infections, and they are controlled by hygiene, vaccination, and isolation of chickens from possible human and animal sources of contamination (Dekich, 1994). A few "old" antibiotics, including tetracyclines, are available for treating bacterial infections, but such actions are uncommon. A large east coast producer treated less than 2 percent of its 7,500 flocks in 1994.

Two antibiotics—virginamycin and bambermicin—are used to promote growth in chickens. Neither is used in human medicine. The dose for growth promotion has remained constant at 1 to 2 grams per ton of feed for 10 years, and the increased growth rate has remained constant. According to a chicken-producing company, the company would discontinue growth promotion use if it did not contribute to profits.

BOX 7–1: Chickens in the United States

The chicken—not the sparrow, pigeon, or starling—is the most common bird on the planet. The United States produces 7 billion chickens annually, or about 29 chickens for every one of the 240 million Americans.

About 20,000 farm families contract with large chicken producers and packers, and the average farm has two chicken houses. Each house produces all of the chicken consumed by 15,000 Americans annually. Production has doubled since 1978, and increases 4 to 5 percent annually.

Pigs—Decreasing Use with Increasing Concentration of Production

The number of pork producers is decreasing and the number of pigs sold by each producer is increasing (National Pork Producers Council, 1994), and antibiotic use appears to decrease with increasing size of pork production operations (Sundberg, 1994). The reasons for the trend are not well known, but better hygiene is believed to account for part of the decrease in subtherapeutic antibiotic use. More generally, larger operations mean that the producer's income is more dependent on pork production, rather than being drawn from several products, say, corn and pigs, and management probably becomes more focused on the animals.

The National Pork Producers Council has produced a Quality Assurance Program (National Pork Producers Council, 1994) that includes guidelines for the use of all drugs, including antibiotics. Those guidelines are intended to prevent the appearance of levels of drugs that exceed federal limits in finished meat products. According to the pork producers council, the percentage of

violations for all drug residues in pork dropped from 10 percent in the mid-1980s to less than 1 percent in 1994.

Trends in Some Other Sectors of Meat Production

During the early 1980s, sales of tetracyclines and penicillin for use in animal feeds slowly declined from 2.9 million kilograms of tetracyclines in 1980 to 2.4 million in 1985 and from 400,000 kilograms of penicillin in 1980 to 300,000 in 1984 (IOM, 1989, chap. IV). No more recent data are readily available.

Levy (1992, p. 142) states that tetracyclines were added to animal feeds for growth promotion at levels of 5 to 10 parts per million in the 1950s (roughly 5 to 10 grams of antibiotic per ton of feed). Currently, concentrations of 50 to 200 parts per million are commonly used. The higher rates of use have not substantially increased production costs because the cost of antibiotics on a weight basis has decreased over the same period. Because of the slim profit margin in meat production, decreased growth promotion effects, coupled with increased costs, could lead to a reduction in subtherapeutic uses of antibiotics as the costs of the drugs approach or exceed the benefits from faster growth.

Summary of Comments on Subtherapeutic Uses of Antibiotics

Levy (1992, p. 156) suggests that several factors are reducing the agricultural uses of antibiotics: increased concerns about drugs of all kinds in food; greater appreciation of the threat of antibiotic-resistant bacteria and the contribution that agricultural use of antibiotics may make to it; better animal husbandry that reduces the need for antibiotics; and legislative and regulatory initiatives. Indeed, FDA experts report that they see few applications for the subtherapeutic uses of new antibiotics (FDA, 1995). While Levy's impressions may be accurate, and decreases in such uses were reported over a decade ago, the phasing out of subtherapeutic uses would not necessarily end the controversy about antibiotic use in animals.

CONTROVERSY OVER FLUOROQUINOLONES IN FOOD PRODUCTION

Just as physicians need new antibiotics to treat human diseases, veterinarians see needs for the use of new antibiotics in their practices. FDA has approved the use of one fluoroquinolone in the treatment of diseases in companion animals, and several manufacturers have requested approvals for the use of fluoroquinolones in the treatment of diseases in food animals. Fluoroquinolone use in animals has been more widespread in Europe, and resistance to the drugs has been reported in bacteria isolated from treated animals.

Because of the importance of fluoroquinolones in medicine, the American Society for Microbiology, the Infectious Diseases Society of America, and officials of the Centers for Disease Control and Prevention have advised FDA to restrict the use of fluoroquinolones in food animals. In particular, the Infectious Diseases Society requested that no formulations of fluoroquinolones in animal feeds be allowed. That request, if honored, would allow veterinarians to treat individual animals, but prevent treatment of herds or flocks. It is opposed by some veterinarians who maintain that using the antibiotic in feed is necessary to treat animals.

FDA has received no applications for the long-term use of fluoroquinolones in agriculture and does not expect to (FDA Veterinarian, 1994), but it held public hearings in May 1994 on possible therapeutic uses. At that meeting FDA announced that it was considering a new policy that would restrict approval of new antibiotics to prescription uses in disease treatment and prevention. The consensus of the advisory panel convened for that study was that the benefits of restricted short-term therapeutic use of fluoroquinolones in food animals outweighed the potential human health risk due to resistant organisms, but that strict controls on usage and improved surveillance were warranted (FDA 1995a).

As therapeutic agents, fluoroquinolones could be used to prevent disease in herds or flocks that are known to contain infected animals. Such preventive use requires formulations of antibiotics that can be incorporated into water or feed, leading to concern that those formulations will find widespread use in growth promotion, exerting heavy selection pressure for the emergence of fluoroquinolone-resistant bacteria. There is a historical base for this concern. Chloramphenicol (CAP) was licensed for therapeutic use in livestock but never for subtherapeutic uses. Nevertheless, veterinarian and husbandry experts published articles that gave details about the use of CAP for growth promotion. As sales soared for such unapproved use, FDA intervened and banned the marketing of oral solutions of CAP that were convenient for treating farm animals. Unlike most antibiotics, CAP causes severe anemias and other diseases of the blood in some humans, increasing concern that any residual CAP in meat might directly harm humans.

At the May 1994 meeting, FDA considered opinions from private organizations and professional societies and other federal agencies that ranged from urging that the fluoroquinolones be completely restricted from agricultural use to arguments that they were necessary for the care of animals and that the risk of resistance from agricultural use paled beside the risk from medical uses. Currently (July 1995) FDA is preparing its policy statement for agricultural uses of fluoroquinolones.

In November 1994, FDA held another meeting about the possible use of surveillance systems to keep track of the emergence of antibiotic-resistant bacteria, including the emergence of fluoroquinolone-resistant bacteria in animals if agricultural uses of those drugs are permitted. FDA is also drafting a statement on surveillance that will consider the questions raised by antibiotic resistance.

REFERENCES

Anderson, E.S. 1968. The ecology of transferable drug resistance in the enterobacteria. *Annual Review of Microbiology 22:*131.

Animal Health Institute. 1995. Personal communication; letter comments on earlier draft of this report. 30 May.

Bates, J., J.Z. Jordens, and D.T. Griffiths. 1994. Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man. *Journal of Antibiotics and Chemotherapy 34:*507–516.

Bywater, R.J., SmithKline Beecham Animal Health, Surrey, United Kingdom. 1995. Personal communication; telephone conversation with M. Gough, OTA. April 20.

Corpet, D.E. 1993. An evaluation of methods to assess the effect of antimicrobial residues on the human gut flora. *Veterinary Microbiology 35:*199–212.

Dekich, M., Purdue Farms, Salisbury, Maryland. 1994. Remarks at U.S. Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 9.

Elder, H.A., I. Roy, S. Lehman, et al. 1993. Human studies to measure the effect of antibiotic residues. *Veterinary and Human Toxicology 35* (Supplement 1):31–36.

Ervik, A., B. Thorsen, V. Eriksen, et al. 1994. Impact of administering antibacterial agents on wild fish and blue mussels *Mytilus edulis* in the vicinity of fish farms. *Diseases of Aquatic Organisms 18:*45–51.

Feinman, S.E. and J.C. Matheson. 1978. *Draft Environmental Impact Statement. Subtherapeutic Antibacterial Agents in Animal Feeds.* U.S. Food and Drug Administration: Rockville, MD.

FDA Veterinarian. 1994. Advisory committees discuss fluoroquinolones. July/August issue, pp. 2–5.

Gorbach, S.L. 1993. Perturbation of intestinal microflora. *Veterinary and Human Toxicology 35* (Supplement 1):15–23.

Hays, V.W. and C.A. Black. 1989. *Antibiotics for Animals: The Antibiotic Resistance Issue. Comments from CAST: 1989-92*. Council for Agricultural Science and Technology: Ames, IA.

Institute of Medicine. 1989. *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed.* National Academy Press: Washington, DC.

Kidd, A.R.M. 1994. *The Potential Risk of Effects of Antimicrobial Residues on Human Gastro-intestinal Microflora.* Fédération Européenne de la Santé Animale: Brussels, Belgium.

Klare, I., H. Heier, H. Claus, R. Reissbrodt, and W. Witte. 1995. *van*A mediated high level glycopeptide resistance in *Streptococcus faecium* from animal husbandry. *FEMS Microbiology Letters 125*:165–172.

Levy, S.B. 1978. Emergence of antibiotic-resistant bacteria in the intestinal flora of farm inhabitants. *Journal of Infectious Diseases 137:*688–690.

Levy, S.B. 1983. Antibiotic-resistant bacteria in food of man and animals. In Woodbine, M. (ed.) *Antimicrobials and Agriculture*. Butterworth: London, pp. 43–61.

Levy, S.B. 1992. *The Antibiotic Paradox.* Plenum Press: New York.

Levy, S.B., G.G. Fitzgerald, and A.B. Macone. 1976. Changes in intestinal flora of farm personnel after introductions of tetracyclines-supplemented feed on a farm. *New England Journal of Medicine 295:*583–588.

Murray, B.E. 1995. Editorial response: What can we do about vancomycin-resistant enterococci? *Clinical Infectious Diseases 20:*1134–1136.

National Pork Producers Council. 1994. *Pork Facts.* National Pork Producers Council: Des Moines, IA.

National Research Council. 1980. *The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds.* National Academy Press: Washington, DC.

Stallones, R.A. 1982. Epidemiology and public policy: Pro- and anti-biotic. *American Journal of Epidemiology 115:*485–491.

Sundberg, P., National Pork Producers Council, Des Moines, IA. 1994. Remarks at U.S. Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 9.

Teske, R.H., Center for Veterinary Medicine, U.S. Food and Drug Administration. 1995. Personal communication. Telephone conversation with M. Gough, OTA. April 21.

U.S. Congress, Office of Technology Assessment. 1979. *Drugs in Livestock Feed.* Washington, DC: U.S. Government Printing Office. [OTA-F-91.]

U.S. Food and Drug Administration. 1995. Comments on earlier draft of this OTA report. Memorandum from Lois Adams, U.S. Food and Drug Administration, to M. Gough, OTA. April 10.

U.S. Food and Drug Administration. 1995a. Comments on second draft of this OTA report. Memorandum from Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration to Office of Technology Assessment. June 16.

U.S. House of Representatives, Committee on Science and Technology, Subcommittee on Investigations and Oversight. 1984. Hearing: *Contract with Seattle.* U.S. Government Printing Office: Washington, DC.

Walker, R., Michigan State University. 1994. Remarks at Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 10.

Appendix A: Coverage of Antibiotic Resistance in the Popular Literature, 1950 to 1994

A

The substance and tone of articles about antibiotic resistance in the popular literature have changed over time (Rosenkrantz, 1995).[1] In the 1950s sobering cautions about the dangers of antibiotic overuse accompanied announcements from medical and scientific experts celebrating reduced mortality from specific diseases. The articles were recast by the mid 1980s. The public was faced with new warnings that bacteria are "winning the race" because they are "smarter" than men. These conclusions are illuminated through the decade-by-decade analysis that follows.

1950 to 1959

In the late 1940s and early 1950s scientific and popular periodicals were generally enthusiastic about the benefits that antibiotics would provide for human health and well-being through better medicine, agriculture, and even home gardening. Public interest can partly be gauged by the range of journals and articles. The *Saturday Evening Post,* as well as *Science,* published articles on streptomycin and tuberculosis; *Reader's Digest* (June 1955) excerpted an article, "Bringing the Antibiotics Up To Date," by Paul DeKruif, a popular science writer and author of *The Microbe Hunters.* But there were also many warnings against false confidence in the continuing usefulness of antibiotics.

Literature is this decade included feature articles about the problems of resistance. The *New York Times* (May 2, 1953) quoted Sir Alexander Fleming, who discounted reports that germs were becoming penicillin resistant and suggested that indiscriminate use led to patient sensitivity. Howard Florey, the English scientist who developed methods for producing penicillin, was quoted in *Newsweek* (Oct. 20, 1958) explaining that *Staphylococcus aureus* itself is not resistant; only certain strains that develop in hospitals produce an enzyme called penicillinase that destroys penicillin.

A reporter covering a U.S. Public Health Service conference on hospital infections wrote that " . . . every week in the year at least one hospital in the cleanest country on earth is threatened with an outbreak of serious 'staph' infections" (*Newsweek,* Sept. 29, 1958). In the same year,

[1] Rosenkrantz, B.G. 1995. Historical Review: Responses to Antibiotic Resistance. Contract Report to the Office of Technology Assessment. Photocopied transcript.

the U.S. Surgeon General announced that overreliance on antibiotics had led to inroads by the "golden staph" [*Staph. aureus*]. The public learned that these germs could be found everywhere. The recommended response for control was hospital hygiene and asepsis, not more antibiotics (*Time*, Mar. 24, 1958).

The popular press pondered the cause of this growing problem. Was it the unjustified or unscientific use of antibiotics, or were medical practitioners taking a "shotgun" approach to therapy? An unnamed surgeon reflected that in his field penicillin was used casually, "like water." An article in *Science News Letter* (1953) was titled "Fear Man-made Epidemics." Scientists were cited explaining that antibiotics should not be used prophylactically in attempts to ward off infection.

At the same time, scientists informed the public about research on the causes of bacterial resistance. *Time* (Mar. 24, 1958; Nov. 17, 1958) reported that microbiologists were divided about whether Staphylococcus develops resistance to antibiotics or whether antibiotics eliminate susceptible Staphylococci, leaving behind the most virulent strains. Although antibiotics might have falsely raised expectations, by the end of the decade most of the popular press did not question the authority of scientists or the capability of science and medicine to continue to make progress in fighting disease.

1960 to 1969

During the 1960s new questions surfaced about the responsibility of government in ensuring the safety and efficacy of pharmaceuticals, and increasing concern about the dangers of bacterial resistance furthered public interest in the development of new antibiotics. In this decade the U.S. Food and Drug Administration (FDA) became more visible to the public; first through Senator Estes Kefauver's hearings on the drug industry, but even more so when the tragedy of thalidomide was narrowly averted in the United States.

For the more informed reader, *Science* (May 26, 1967) explained how "R factors" (now called plasmids) mediated resistance, and *Newsweek* (Aug. 22, 1966) introduced scientific language to explain that "resistant bacteria can pass their R factors along to bacteria of other strains," emphasizing the specific dangers posed by mutant *Escherichia coli* from cattle fed antibiotic-laced feed. Perhaps to appear evenhanded, the same article implied that an editorial in the *New England Journal of Medicine* warning about the dangers of indiscriminate antibiotic use might be overdramatic. *Good Housekeeping* (August 1961; January 1964) warned that antibiotics were never to be used casually for minor ailments. In the early 1960s, the *New York Times* published reports of a steady increase in antibiotic-resistant hospital infections (Mar. 12, 1961; Feb. 25, 1962; Sept. 28, 1962).

Despite the introduction of new antibiotics, and the promise of more yet to be identified, the popular press cautioned that specific criteria should be used to determine which drugs are effective in treating each disease. The science editor and editorial board of the *New York Times* (Sept. 9, 12, 14, 1966; Nov. 21, 23, 1969) produced a series on the transmission of antibiotic resistance among bacteria. Resistance was described as a widespread peril that could be spread by "mating" among different bacteria.

In 1967 the *New York Times* reported that, in comparison to Great Britain, the United States was slow to control use of antibiotics in agriculture, a lapse that could exacerbate resistance (*New York Times*, June 11, 1967). Newspapers covered the tensions in the debate among interested parties, including: recommendations generated by FDA and the National Research Council of the National Academy of Sciences regarding limiting antibiotics in animal feed; skepticism registered by pharmaceutical firms about the significance of antibiotic resistance; and warnings by the meat industry about potential price increases should antibiotic protection of herds be prohibited (*New York Times*, Sept. 22, 1966; June 11, 1967).

1970 to 1979

In the 1970s the periodical press turned sympathetically to physicians for their perspectives on the conflicting benefits and dangers of antibiotics. *McCalls'* (October 1976) regular physician columnist Dr. William Nolen authored "Antibiotics: What They Will and Won't Cure," and focused on the therapeutic limitations of antibiotics, but he did not raise the complications of antibiotic resistance. Other periodicals focused on the fundamentals of bacterial genetics. *Newsweek* (June 19, 1978), in its regular coverage of medical news, directed attention to hospital "mini-epidemics" and the new medical specialty, infection control, that brought doctors, nurses, technicians and epidemiologists to the scene. Attention to antibiotic resistance was also more frequent in articles on agriculture, and in these reports both pharmaceutical and agricultural interests were identified as enemies of regulation.

Accounts of bacterial resistance available to the general reader varied, sometimes framed in dramatic language that emphasized the emergence of "super bugs" like the "Andromeda strain," and at other times presenting detailed reports of scientific meetings (*New York Times*, Oct. 15, 18, 1970; Feb. 6, 1972; Mar. 3, 1975). Concerns about the consequences of indiscriminate use of antibiotics were reflected in a Senate Health Subcommittee finding "that drug companies over-promote antibiotics to physicians and physicians overprescribe them, especially for colds and other viral infections that antibiotics can't counter" (*Science News*, May 27, 1972). Information on the basic mechanics of "Transmissible Multiple Drug Resistance" (*Science*, May 19, 1972) became increasingly sophisticated in *Science*, *Scientific American*, and *Science News*. *Good Housekeeping* (March 1975) reported that the American Medical Association had discovered that resistant organisms, once largely confined to hospitals, were now also found in the community.

Reflecting a general frustration, the *New York Times* (July 16, 1971) reported on a 25-year survey of health care that found despite "spectacular scientific advances. . .many diseases that should no longer exist, such as TB, still do." Data from the CDC reported pneumonia and gonorrhea resistance to antibiotics. A CDC research team estimated that 22 percent of antibiotic use in the hospital was unnecessary and led to "superinfection" (*New York Times*, Jan. 28, 1976; Nov. 10, 1976).

The FDA proposed policies (congruent with Britain and other European countries) to limit antibiotics in animal feed and reported that animals consumed more than 40 percent of the antibiotics produced. In a replay of an article that had appeared in the late 1960s, *Time* (Sept. 10, 1979) reported that the FDA-proposed limits were opposed "by a coalition of pharmaceutical manufacturers and farming interests." Congress agreed "to stay any action pending further studies."

1980 to 1994

Reports of emergent and re-emergent diseases have often implicated antibiotic resistance. Tuberculosis, once slated for virtual eradication in the United States by the early 21st century, proved impossible to eliminate, and its persistence was linked to premature budget cuts in the nation's public health efforts. But the blame for the re-emergence of tuberculosis was spread broadly. New cases of tuberculosis were often associated with homeless populations or with immigrants from areas of the world where the disease was endemic (*New York Times*, July 26, 1980, June 18, 1985); reportedly, attempts to control tuberculosis were exacerbated by patients' failure to comply with extended treatment, which could lead to multi-drug-resistant disease.

In the 1980s epidemiologic and comparative international perspectives on antibiotic resistance became prominent for the first time. In 1981 doctors in medical teaching centers called for international controls "to halt 'indiscriminate' use of antibiotics" (*New York Times*, Aug. 6, 1981). Broader concern was reflected in reports from prominent spokespersons for the international

scientific and medical communities, as well as in reports of the dangers to Americans from multiple-drug-resistant organisms imported as a result of increased world travel, and via immigrants (often illegal) from developing countries.

Some diseases once treated by antibiotics were reportedly now out of control. CDC reports on the rise of antibiotic-resistant gonorrhea, streptococci, and hemophilus infections brought the danger closer to home when they were connected to children's ear infections and to the overwhelming (not antibiotic-resistant) infection that killed the Muppets creator, Jim Henson (*New York Times*, Feb. 23, 1989; May 8, 18, 1990; Jan. 28, 1992). The emphasis and tone of reporting on antibiotic-resistant bacteria shifted, markedly influenced by accounts of how infectious disease strikes back in the war between pestilence and people (*Time*, Sept. 12, 1994).

Time reported that the rising tide of antibiotic resistance affected "nearly every disease organism known to medicine"; the "microbe's extraordinary ability to adapt" was "a fact of life." The magazine reported that adaptation was "written into evolution," but few anxieties were relieved by reassurances that microorganisms were only "trying to. . . survive and reproduce, just as we are" (*Time*, Sept. 12, 1994).

Readers of popular magazines were challenged by articles such as "Are you **overdosing** on antibiotics?" (*Redbook*, December 1991). There was mounting tension between warnings of dangers from "the ghost of scourges from the past" *(U.S. News and World Report*, Oct. 26, 1992) and reports of FDA approvals of new antibiotics. As in the 19th century, doctors cautioned that "A Hospital is No Place for a Sick Person To Be" (*Discover*, October 1985), and patients feared that "Hospitals May Be Breeding Grounds" (*USA Today*, February 1991), as evidence mounted that "Hospitals Can Make You Sick" (*World Press Review*, August 1988).

Scientists and physicians were quoted in desperate moments as they drew dire conclusions for the future. A feature article, "The End of Antibiotics," quoted one physician's explanation that "microorganisms are winning" because "they are so much older than we are . . . and wiser" (*Newsweek*, Mar. 28, 1994). With no new antibiotics ready for introduction and evidence of the existence of "smart bugs" that carry information in resistance genes, attention to misuse of antibiotics in medicine and agriculture competed for blame with human populations which were likened to hothouses for breeding of germs. Some reports downplayed professional accountability, shifting responsibility to social changes that included the spread of AIDS, the rise in homelessness, the proliferation of child care centers, the influx of immigrants, increases in international travel, and the disturbance of ecosystems in both economic development and recreation (*U.S. News and World Report*, Oct. 26, 1992).

A change of tone and target appeared in the 1980s. Partly as a consequence of lessons in immunology that accompanied publicity on AIDS, but also because bacterial genetics had become a growth industry, reports of new evidence on antibiotic resistance used adaptations of everyday language and diagrams to explain resistance genes to the public. Bacteria acquired identities of their own. They were pictured or perceived as willful beings governing their own mutations and transferring resistance genes to other bacteria in conscious efforts to outwit humans and their antibiotics. Journalists quoted scientists describing "bugs" with a crafty intelligence capable of becoming relentless demons.

Comments on the Popular Literature

Penicillin marked the beginning of a new era for most Americans and a majority of people around the world. However, from its very beginning the triumph of antibiotics was accompanied by fear that resistance might reverse the advantages gained over infections. Anxiety was expressed as concern that ordinary germs would take revenge, that miracle drugs were a two-edged sword, eliminating some bacteria and favoring others.

Over time the early warnings transformed into forecasts of apocalypse. Penicillin had not banished hospital infections as had once been

dreamed; instead, first "staph" and then other organisms became resistant. Unexpected disease and death spread among patients despite the efforts of infectious disease experts. Scientists discovered that bacterial resistance to antibiotics was transmitted among disease-bearing organisms in ways that were unimaginable before the availability of the tools of molecular biology. Scientists collaborated with journalists to instruct the public in the new language of resistance genes, and the American public read about unexpected outbreaks of untreatable mysterious infections in the 1960s and 1970s. But the 1980s appeared more dangerous yet. AIDS laid the groundwork for new fears, and fatal multiple-drug-resistant tuberculosis and streptococcal pneumonia put medical news and the terms "emergent" and "re-emergent" disease on the front page of newspapers and on bestseller lists.

According to Rosenkrantz (1995), the emergence or control of antibiotic resistance was posed first as a contest between knowledge and ignorance, then between control and irresponsibility, and ultimately between good and evil. The 1990s saw the stream of scientific and medical information merge with fears about social disorder and political corruption. The bearers of the new threat were often immigrants from Asia, Africa, and South America, where AIDS, tuberculosis, and other infectious diseases were prevalent and where antibiotics were unavailable or improperly used. The homeless, who failed to comply with treatment plans, were blamed for the spread of antibiotic-resistant tuberculosis. Child-care centers and hospitals were singled out as places that spawn antibiotic resistance. But blame was not restricted to the powerless. Pharmaceutical firms and agribusiness were also incriminated on the basis of alleged irresponsibility and greed. Attributing the spread of antibiotic resistance to victims of disease as well as to representatives of corporate power accentuated public anxiety and seemingly placed control outside the realm of science. Meanwhile, it appears that fear of antibiotic-resistant disease has not eroded public demand for antibiotics. The placing of blame on the most vulnerable and the most powerful may have compromised the impetus for controlling patients' inappropriate requests for antibiotic prophylaxis and therapy.

The problems with antibiotic-resistant bacteria are not new to this decade or even to this generation. Such bacteria were identified soon after the first use of antibiotics, and the technical and popular press has reported on them and the problems with which they are associated. Over the last 50 years, warnings have been voiced about inappropriate antibiotic use—too frequently demanded by patients, too heavily prescribed by physicians, too heavily used in agriculture, and too often used when they have no effect. The variety of possible explanations for the emergence of this public health problem highlights the complexity of the issues and also provides a number of approaches to control the problem, which are discussed elsewhere in this OTA report.

Appendix B: Glossary B

Active Efflux: a major mechanism of bacterial resistance in which an antibiotic is pumped out of the bacterial cell.

Active Immunization: the process of administering specific microbial antigens that stimulate the host's immune system to produce protective antibodies, "vaccination."

Agar Dilution Test: one of four diagnostic methods currently used to determine the antibiotic susceptibility or resistance of bacteria. See also *agar gradient test, broth dilution test,* and *disk diffusion test.*

Agar Gradient Test: one of four diagnostic methods currently used to determine the antibiotic susceptibility or resistance of bacteria. See also *agar dilution test, broth dilution test,* and *disk diffusion test.*

Aminoglycosides: a family of bactericidal antibiotics that block bacterial protein synthesis by binding to the small subunit of the bacterial ribosome; examples are streptomycin, kanamycin, neomycin, gentamicin, amikacin, and tobramycin.

Amoxicillin: a broad-spectrum β-lactam antibiotic drug.

Antibacterial: a drug that kills or inhibits the growth of bacteria.

Antibiogram: a guide produced by a microbiology laboratory for physicians' use that profiles the susceptibility of commonly encountered bacteria to various antibiotics.

Antibiotics: a class of substances that can kill or inhibit the growth of some groups of microorganisms. Used in this report to refer to chemicals active against bacteria. Examples are penicillin, tetracycline, erythromycin, and cephalosporins. Originally antibiotics were derived from natural sources, e.g., penicillin from molds, but many currently used antibiotics are semi-synthetic and modified with additions of man-made chemical components. See *antimicrobials.*

Antibiotic Resistance: a property of bacteria that confers the capacity to inactivate or exclude antibiotics or a mechanism that blocks the inhibitory or killing effects of antibiotics.

Antibiotic Susceptibility: the opposite of resistance and applies to bacteria that are killed or inhibited by an antibiotic. Susceptibility to a particular antibiotic does not mean that the bacteria are susceptible to all antibiotics.

Antigen: a chemical structure on or in a cell that is recognized by the immune system. The

immune system produces antibodies that react with the antigens.

Antigen Test: a diagnostic method for detecting the presence of a specific chemical structure. As used here, it is a test for detecting the presence of specific bacteria.

Antimicrobials: a class of substances that can destroy or inhibit the growth of bacteria; examples are sulfonamides. See *antibiotics.*

Anti-Sense: DNA is a helical molecule with two strands. One strand, the "sense" strand, is used in the synthesis of RNA and protein; the other strand, the "anti-sense" strand, serves a structural purpose in DNA but not in RNA synthesis.

Anti-Sense Oligonucleotide: a length of the anti-sense strand of DNA prepared to bind specifically to a target stretch of DNA.

Bacteremia: a pathologic state characterized by the presence of bacteria in the blood.

Bacteria: microscopic, single-celled organisms that have some biochemical and structural features different from animal and plant cells.

Bactericidal: a term for agents that kill bacteria.

Bacteriophage: see *phage.*

Bacteriostatic: a term for agents that inhibit bacterial growth.

Beta-Lactam Antibiotics: the most widely used class of antibiotics which includes penicillins, cephalosporins including ceftriaxone and ceftazidime, carbapenems, monobactams, and imipenem. β-lactam antibiotics act by inhibiting the synthesis of peptidoglycan—the major component of a bacterial cell wall.

Beta-Lactamase: an enzyme produced by some bacteria that degrades beta-lactam antibiotics. See *penicillinase.*

Breakpoint: a concentration of antibiotic that marks the division either between the resistant and intermediate response or between the intermediate and susceptible response using antibiotic susceptibility tests.

Broad-Spectrum Antibiotic: an antibiotic effective against a large number of bacterial species; generally describes antibiotics effective against both Gram-positive and Gram-negative bacteria.

Broth: a sterile nutrient growth medium used to grow bacteria.

Broth Dilution Test: one of four diagnostic methods currently used to determine the antibiotic susceptibility or resistance of bacteria. See also *agar dilution test, agar gradient test,* and *disk diffusion test.*

Broth Microdilution Test: a miniaturized version of the broth dilution test that uses a test plate with small-sized wells that hold a small volume (about 0.1 milliliters) of broth.

Cecropin: a peptide from the North American silk moth *Hyalophora cecropia* that increases bacterial permeability and can cause bacterial death.

Cell Culture: propagation of cells in a laboratory environment.

Chromosome: used in this report to refer to the circular DNA that contains the genes for the functioning of a bacterium.

Clinical Trial: used in this report to refer to research to establish the safety and efficacy of a drug such as an antibiotic.

Colonization: capacity of a bacterium to remain at a particular site and multiply there.

Commensals: bacteria that live on the skin, in body orifices, or the intestines, and do not usually cause disease, and may be beneficial to the host organism.

Conjugation: the process by which DNA is transferred from one bacterium to another that involves cell-to-cell contact.

Defensin: a peptide from mammalian cells including epithelial cells lining the human small intestine that increases bacterial permeability and can cause bacterial death.

Deletion Mutation: a mutation that results in loss of a length of DNA from the chromosome.

Disk Diffusion Test: one of four diagnostic methods currently used to determine the antibiotic susceptibility or resistance of bacteria. See also *agar dilution test, agar gradient test,* and *broth dilution test.*

DNA (deoxyribonucleic acid): the substance of heredity; a nucleic acid that is found in the cell nucleus that carries the genetic information necessary for all cellular functions.

DNA Probe Assay: a new diagnostic method for identifying the presence of bacteria by using fragments of DNA or RNA (probes) that bind to target bacterial or resistance gene DNA or RNA sequences.

Efficacy: used in this report to refer to the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under defined conditions of use.

Empiric Therapy: used in this report to describe antibiotic treatment based on signs and symptoms of disease and in absence of knowledge of the causative agent of infection.

Enterococcus: bacteria normally found in the intestinal tract and genitourinary tract. Some strains are pathogenic and a few are resistant to all available antibiotics, including vancomycin.

Enzymatic Test: a diagnostic method of testing for antibiotic resistance that directly measures the presence of an enzyme that confers resistance in a bacterium.

Escherichia coli: a commensal bacterium that lives in the intestine, a workhorse of biotechnology, and sometimes a cause of opportunistic infections.

Eukaryote: a cell or organism with membrane-bound, structurally discrete nuclei, and well-developed cell organelles. Eukaryotes include all plants, animals, and fungi. Compare *prokaryote.*

Expression: functioning of a gene, generally measured by the amount of gene product (usually a protein or nucleic acid) made by the cell. See *gene expression.*

Flora: the populations of commensal bacteria normally present in the intestine, body orifices, and on the skin.

Fluorometer: an optical device more sensitive than the human eye to detect the presence or absence of growth of bacteria in microdilution tubes. See *broth microdilution test.*

Formularies: a listing of approved drugs for various medical indications originally created as a cost-controlling measure, but used more recently to guide use of antibiotics based on information about resistance patterns.

Fungus: member of a class of relatively primitive organisms; includes mushrooms, yeasts, rusts, molds, and smuts.

Gene: a unit of heredity; a segment of the DNA molecule that carries the directions for the structure of a given protein.

Gene Expression: activity of a gene measured by the amount of gene product (usually a protein or nucleic acid) made by the cell.

Genetic Recombination: the process by which separate lengths of DNA from different sources are chemically joined to produce new genetic combinations.

Glycopeptides: compounds made up of amino acids and sugars that may have antibacterial activity; vancomycin and teichoplanin are glycopeptide antibiotics.

Gram's Stain: a bacteriological stain used to determine a major division between bacterial species; the reaction depends on the complexity of the cell wall. Bacteria that retain the gram stain (blue) are Gram-positive; bacteria that lose the gram stain but stain with a counterstain (red) are Gram-negative.

Haemophilus influenzae: a commensal bacterium commonly found in the upper respiratory tract capable of causing infections such as otitis media, sinusitis, conjunctivitis, bronchopneumonia and type b meningitis.

Immunosuppression: inhibition or suppression of the normal immune response, as a result of giving drugs to prevent transplant rejection, of irradiation or chemotherapy, or of some infections as in AIDS.

Incidence: the frequency of new occurrences of disease within a defined time interval. Incidence rate is the number of new cases of a specified disease divided by the number of

people in a population over a specified period of time, usually one year.

Infection: successful colonization on a site of the body by a microorganism capable of causing damage to the body.

Insertion Mutation: a mutation that adds a length of DNA to an existing DNA molecule.

Integron: DNA segment that can carry multiple antibiotic resistance genes and that can insert in plasmid and chromosomal locations.

Intermediate Resistance: In some cases, resistance to an antibiotic emerges in incremental steps, so some bacteria have "intermediate" resistance and can survive and grow in low concentrations but not higher concentrations of an antibiotic.

Invasive: of a bacterium, (1) capable of penetrating the host's defenses; (2) capable of entering host cells or passing through mucosal surfaces and spreading in the body.

In-vitro Tests: techniques that use cells, tissues, or explants grown in a nutritive medium rather than using living animals or human subjects.

In-vivo Expression Technology (IVET): techniques that identify bacterial genes that are expressed only when the bacteria are in the host.

Isolate: to establish a pure culture of a microorganism.

Lactoferrin: the second most abundant protein in human milk; found to have antibacterial activity.

Macrolides: a family of bacteriostatic antibiotics that inhibit protein synthesis by binding to the large subunit of the bacterial ribosome; include erythromycin, clindamycin, chloramphenicol (rarely used because of adverse side effects), and the new drugs clarithromycin and azithromycin.

Magainins: short peptides, taken from the skin cells of frogs, that increase bacterial permeability by inserting into the bacterial cell membrane that can lead to death of the bacterial cells.

MDR-TB: multi-drug-resistant tuberculosis.

Methicillin-Resistant *Staphylococcus aureus* (MRSA): strictly speaking, a bacterial strain resistant to methicillin. In practice, MRSAs are generally resistant to many antibiotics and some are resistant to all but vancomycin.

Microorganism: minute, microscopic or submicroscopic living organisms; includes bacteria, fungi, and protozoa. Viruses are often included in this category, but they are incapable of growth and reproduction outside of host cells, and some experts insist they should not be classified as organisms.

Minimum Inhibitory Concentration (MIC): the lowest concentration of antibiotic that prevents growth of a bacterium.

MRSA: See methicillin-resistant *Staphyloccus aureus*.

Multiple Resistance or Multiple Drug Resistance: applies to bacteria that are resistant to more than one antibiotic.

Mutation: a genetic change; can occur either randomly or at an accelerated rate through exposure to radiation or certain chemicals (mutagens); may lead to a change in the structure of the protein coded by the mutated gene.

Mycobacteria: bacteria that have cell wall structures different from other bacteria. *Mycobacterium tuberculosis* is the cause of tuberculosis.

Narrow-Spectrum Antibiotic: an antibiotic effective against a limited number of microorganisms; often applied to an antibiotic active against either Gram-positive or Gram-negative bacteria.

Natural Selection: process by which ancestral species of animals and plants evolve into new species.

Nosocomial Infection: infection acquired during hospitalization that is neither present nor incubating at the time of hospital admission unless related to prior hospitalization and that may become clinically manifest after discharge from the hospital.

Notifiable Disease: a disease that physicians are required to report to State health departments.

Oligosaccharides: ("oligo," a few; "saccharides," sugars). Specific oligosaccharides are present on the surfaces of cells in different organs and tissues.

Opportunistic Infection: an infection caused by an organism that does not usually trouble people, such as a commensal bacterium.

Oxacillin: a semi-synthetic penicillin similar to methicillin.

Parasite: an organism living in or on an organism of another species (its host), obtaining part or all of its subsistence from it without rendering any service in return.

Pathogen: an organism that is capable of causing disease.

Pathogenicity: capacity to cause disease.

Penicillin: the first true antibiotic.

Penicillinase: an enzyme which degrades penicillin so that it has no effect on bacteria. See *beta-lactamase.*

Peptides: small protein molecules. Most of interest in this report are peptides from bacteria and from human, frog, shark, rabbit, and moth cells that have been shown to inhibit the growth of or kill some bacteria by breaking down their permeability barriers to the entry of antibiotics. See *magainins, cecropin,* and *defensin.*

Peptidoglycan: a complex polymer of sugars and amino acids that form the major component of the bacterial cell wall.

Phage: a virus that infects bacteria.

Phage Therapy: the use of viruses that attack bacteria to treat disease; an "old" and currently unused therapy.

Plasmid: a circular piece of DNA not associated with the chromosome found in the cytoplasm and capable of replicating and segregating independently. Many plasmids can be spread through bacterial populations by conjugation, and many of the antibiotic-resistance genes of clinical significance are carried by plasmids.

Point Mutation: a "single letter" mutation consisting of an alteration in a single nucleotide in DNA.

Polymerase Chain Reaction (PCR): a laboratory procedure that produces millions of copies of DNA from one or a few molecules.

Preclinical Test: animal studies of drugs before they are tested in human beings.

Prevalence: refers to the total number of cases (new as well as previous cases) of a disease during a designated time period.

Prokaryote: an organism lacking cell organelles and whose DNA is not enclosed within a membrane-bound, structurally discrete nucleus. Bacteria and blue-green algae are prokaryotes. (Some experts consider "blue-green algae" to be better classified as "blue-green bacteria.") Compare *eukaryote.*

Prophylactic Antibiotic Therapy: the administration of antibiotics before evidence of infection and intended to ward off disease.

Protozoa: single-celled animals with membrane-bound organelles.

Quinolones: a class of purely synthetic antibiotics that inhibit the replication of bacterial DNA; includes ciprofloxacin and fluoroquinoline.

Resistance: see *antibiotic resistance.*

Rifampin: an antibiotic that blocks transcription, e.g. synthesis of RNA; its principal use is in treatment of tuberculosis.

Selective Pressure: used in this report to refer to the selection of antibiotic-resistant bacteria through the use of antibiotics. Susceptible bacteria are killed or inhibited, and resistant ones are selected.

Self-Limiting: of an infection, one that proceeds to a point and no further.

Semi-Synthetic Antibiotics: antibiotics derived in part from natural products produced by an organism and in part from synthetic components. Examples are methicillin, nafcillin and cloxacillin.

Sepsis: a state characterized by the presence of pathogenic microorganisms and their products into the bloodstream.

Serum Therapy: the use of fractions of blood from infected animals to treat human disease; an "old" therapy with limited use. Cur-

rently used for the treatment of tetanus and botulism (and snakebites).

Service Laboratory: a commercial microbiology laboratory to which physicians send clinical specimens for analysis.

Squalamine: a steroid compound, closely related to cholesterol, with antibacterial activity. Testing of squalamine is at the preclinical stage.

Staphylococcus aureus: Normally commensal bacteria on the skin that can cause nosocomial infections when they penetrate into body tissues and organs as a result of wounds and surgery. See *MRSA.*

Steroids: natural compounds; the best known is cholesterol. Some steroids isolated from various organs of sharks have been shown to have antibacterial characteristics.

***Streptococcus pneumoniae* or "Pneumococcus" bacteria:** the most common cause of bacterial infection in the United States.

Streptogramin: a new antibiotic, now in phase III clinical trials, effective against some antibiotic-resistant bacteria, including some strains of VRE.

Structure-Based Drug Design: a method of antibiotic research that focuses on an understanding of the ligand:receptor interaction that occurs at the "active site" where the "ligand," in this case the antibiotic, binds to some structure, the "receptor" in the bacteria. Research tools such as X-ray crystallography, nuclear magnetic resonance spectroscopy, and supercomputer combinatorial chemistry are used to design new compounds that will bind more tightly to the "active site."

Sulfa Drugs: a group of synthetic chemicals that inhibit bacterial growth and metabolism. See *sulfonamide.*

Sulfonamide: the first antibacterial drug that was not overly toxic to humans. It is a synthetic, antimicrobial (rather than antibiotic) drug.

Surveillance Systems: used in this report to refer to data collection and record keeping to track the emergence and spread of disease-causing organisms such as antibiotic-resistant bacteria.

Susceptibility Test: any of a large number of tests used to determine if bacteria are susceptible or resistant to an antibiotic.

Systemic: pertaining to or affecting the body as a whole; frequently applied to bloodstream infections.

Target Amplification Method: methods to increase the number of target DNA sequences through such methods as polymerase chain reaction (PCR). See *polymerase chain reaction.*

Tetracyclines: a family of broad-spectrum antibiotics used in the therapy of infections caused by Gram-positive and Gram-negative bacteria.

Toxicity: the quality of being poisonous. Referring to antibiotics, the degree to which they produce unwanted, adverse effects.

Transcription: synthesis of RNA from a DNA template.

Transduction: transfer of bacterial genes from one bacterium to another by a bacterial virus (called a phage).

Transformation: uptake by a bacterium of DNA from a ruptured cell and incorporation of genes from the DNA into the bacterial chromosome.

Transposons: small, mobile DNA sequences that can move around chromosomes and plasmids. Often they carry genes specifying antibiotic resistance.

Treponema pallidum: bacteria that cause syphilis.

Trimethoprim: an antibiotic administered in combination with a sulfonamide in the treatment of urinary tract infections.

Vaccine: a preparation of living, attenuated, or killed bacteria or viruses, fractions thereof, or synthesized antigens identical or similar to those found in the disease-causing organisms, that is administered to raise immunity to a particular microorganism.

Vancomycin: a widely used glycopeptide antibiotic, particularly important for treatment of infections caused by strains of *Staphylococ-*

cus aureus some of which are resistant to all other antibiotics.

Vancomycin-Resistant Enterococcus (VRE): a bacterial strain. Some VREs are resistant to all commercially available antibiotics.

Virulence: a measure of the degree and severity of pathogenicity of a disease-causing organism.

Virus: submicroscopic pieces of genetic material (RNA or DNA) enclosed in a protein coat that cause infectious disease. Viruses are obligate parasites that can reproduce only in living cells.

Zone of Inhibition: area of no bacterial growth around a disk containing antibiotic; used to measure the antibiotic susceptibility or resistance of bacteria. See *disk diffusion test.*

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