

# Summary, Conclusions, Issues and Options | 1

## SUMMARY

**A**s 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.<sup>1</sup> 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.

<sup>1</sup> 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 accu-

rately 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.<sup>2</sup> 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 *Staphylo-*

*coccus 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.

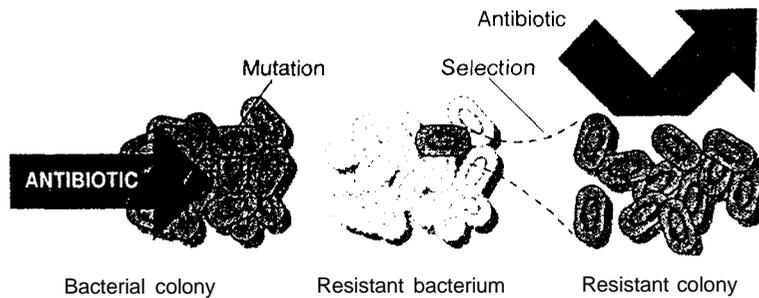
“Antibiotic-resistant bacteria” are strains of bacteria that were once susceptible to an antibiotic but have since acquired resistance after the introduction of antibiotics into medical practice. Antibiotic resistance operates through one of four general mechanisms. The resistant bacterium: 1) does not 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

<sup>2</sup> 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).

## 4 Impacts of Antibiotic-Resistant Bacteria

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 anti-

biotic 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.

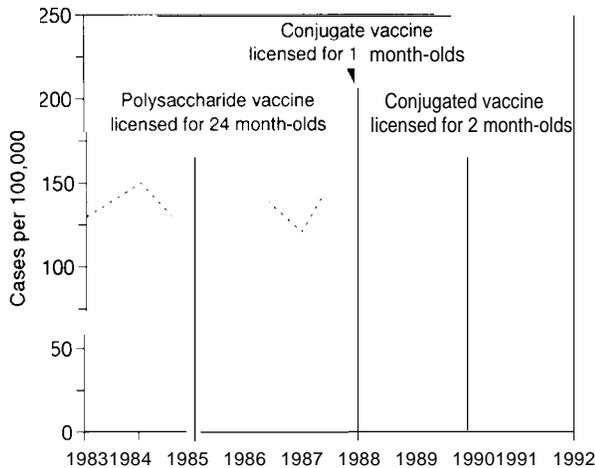
### ***Infection Control***

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-

## 10 Impacts of Antibiotic-Resistant Bacteria

**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 “over-use” 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 *Hemophilus influenzae* type b (Hib), *Neisseria meningitidis*, or *Streptococcus 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 instruc-

tions 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	<i>Penicillin notatum</i>	Used since 1940s
	Semi-synthetic penicillins	Methicillin Piperacillin	Semi-synthetic penicillin derivatives	In use since 1960s; among the most widely prescribed antimicrobials
	Cephalosporins	Cephalexin	<i>C. acremonium</i>	Widely used class of antibiotics
	Carbapenems	Imipenem	Derived from thienamycin, a compound produced by <i>Streptomyces catleya</i>	In use; wide spectrum (active against many species of bacteria including cephalosporin-resistant Enterobacteriaceae)
	Monobactams	Aztreonam	Derived from a compound produced by <i>Chromobacterium violaceum</i>	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) Subtraction (used with ampicillin) Tazobactam sodium (used clinically with piperacillin)	<i>Streptomyces clavuligerus</i>  Semi-synthetic penicillin derivative Semi-synthetic penicillin derivative	Used since 1970s; clavulanate combinations used for wide range of disorders Similar to amoxicillin/clavulanate Tazobactam/piperacillin effective against intra-abdominal infections
	Vancomycin	Vancomycin	<i>Strep. orientalis</i>	Introduced in 1956; used against staphylococcal and enterococcal infections
	Teicoplanin	Teicoplanin	<i>Actinoplanes teichomyceticus</i>	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 sulfonamides
	Protein synthesis inhibitors	Aminoglycosides	Streptomycin	<i>Streptomyces griseus</i>	In use since 1940s; important class of antibiotics
			Kanamycin	<i>Streptomyces kanamyceticus</i>	
Tobramycin			<i>Streptomyces tenebrarius</i>		
Gentamicin			<i>Micromonospora purpurea</i> and <i>echinospora</i>		
Fusidanes	Fucidin		Sodium salt of fusidic acid, derived from the fungus <i>Fusidium coccineum</i>	In clinical use since 1962, but not available in US (except through compassionate release); active against some strains of methicillin-resistant <i>Staph. aureus</i> (MRSA)	
Tetracyclines		Chlortetracycline	<i>Streptomyces aureofaciens</i>	First introduced in 1948, found by screening soil samples for antibacterial activity	
		Oxytetracycline	<i>Streptomyces rimosus</i>		
		Minocycline	Semi-synthetic derivative		
		Doxycycline	Semi-synthetic derivative		

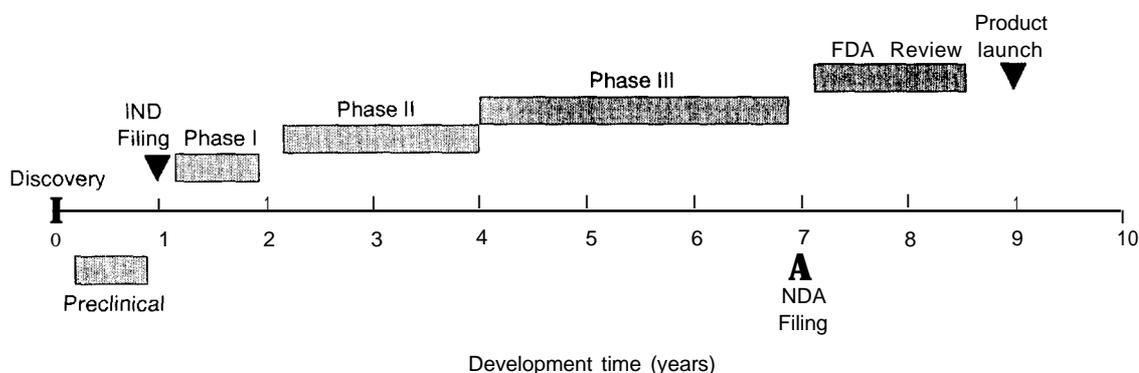
(continued)

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

Action	Family/Class	Example(s)	Source	Status
	Chloramphenicol	Chloramphenicol	<i>Streptomyces venezuelae</i>	First introduced in 1949, currently second line antibiotic because of side effect of aplastic anemia
	Macrolides Azalides	Erythromycin Azithromycin	<i>Streptomyces erythreus</i> semi-synthetic derivative of erythromycin	Discovered in 1952 Available in 1992
	Lincosamides	Clindamycin	Semi-synthetic derivative of lincomycin derived from <i>Streptomyces lincolnensis</i>	Available since the mid 1960s; active against aerobic bacteria
	Mupirocin	Mupirocin	<i>Pseudomonas fluorescens</i>	Introduced in the mid 1980s; topical antibiotic
Interference with RNA synthesis	Rifamycins	Rifampin	<i>Streptomyces mediterranei</i>	First isolated in 1957, important tuberculosis drug
Toxic effect through DNA binding	Nitroimidazoles	Metronidazole	Synthetic	Introduced in 1959, active against anaerobes such as <i>B. fragilis</i>
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) Ethambutanol	Synthetic Synthetic Synthetic	Shown to be effective in 1952 Important tuberculosis drug since 1980 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 annually,<sup>3</sup> 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-

<sup>3</sup>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 use-

ful 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 inter-

ested 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.