Chapter **55**

# Drug Resistance

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The control of infectious diseases is seriously threatened by the steady increase in the number of micro-organisms that are resistant to antimicrobial agents—often to a wide range of these agents. Resistant infections lead to increased morbidity and prolonged hospital stays, as well as to prolonged periods during which individuals are infectious and can spread their infections to other individuals (Holmberg, Solomon, and Blake 1987; Rubin and others 1999). The problem is particularly severe in developing countries, where the burden of infectious diseases is relatively greater and where patients with a resistant infection are less likely to have access to or be able to afford expensive second-line treatments, which typically have more complex regimens than first-line drugs. Furthermore, the presence of exacerbating factors, such as poor hygiene, unreliable water supplies, civil conflicts, and increased numbers of immunocompromised patients attributable to the ongoing HIV epidemic, can further increase the burden of antimicrobial resistance by facilitating the spread of resistant pathogens. In this chapter, we discuss the causes and burden of drug resistance and evaluate interventions that address the resistance problem in developing countries. Although a number of the interventions we discuss are relevant to drug resistance in HIV/AIDS and other forms of antiviral resistance, chapter 18 includes a more in-depth discussion of this subject.

## RISK FACTORS

### Drug Use in Humans

The evolution of drug resistance is facilitated by a number of factors, including increasing use of antibiotics and antimalarials; insufficient controls on drug prescribing; inadequate compliance with treatment regimens; poor dosing; lack of infection control; increasing frequency and speed of travel, which lead to the rapid spread of resistant organisms; and insufficient incentives for patients, physicians, or even governments to care about increasing resistance. It is important to distinguish between risk factors for the emergence of resistance (*de novo resistance*) and those for the spread of resistance (*primary resistance*).

The molecular basis of resistance may give a clue to the likelihood of resistance emerging. If a single DNA base pair mutation leads to the development of resistance, then its selection is likely to be widespread, especially if the biological fitness cost of the mutation is low. De novo or acquired resistance results in the appearance of a resistant strain in a single patient. Subsequent transmission of such resistant strains from an infectious case to other persons leads to disease that is drug resistant from the outset, a phenomenon known as primary resistance (IUATLD 1998). Independent, cumulative events result in multidrug-resistant bacteria or tuberculosis (MDR-TB). Both the creation and the transmission of drug resistance contribute to its prevalence in a given population. This mechanism also holds true in the case of antimalarials; that is, resistance develops when malaria parasites encounter drug concentrations that are strong enough to eradicate the susceptible parasite population, but they fail to inhibit the multiplication of naturally occurring resistant strains. Commonly used antimalarial drugs are not mutagenic.

In the case of tuberculosis, spontaneous mutations leading to drug resistance occur rarely in *Mycobacterium tuberculosis,*

and multidrug regimens can prevent the emergence of clinical drug resistance (Cohn, Middlebrook, and Russell 1959). Resistance is thus an avertable phenomenon resulting from inadequate treatment, which, in turn, is often the result of an irregular drug supply, prescription of inappropriate regimens, or poor adherence resulting from a lack of supervision. In the case of malaria, the widespread misuse of chloroquine as prophylaxis is believed to be an important factor in the emergence and spread of resistance to this drug.

Despite conventional wisdom, the highest rates of antibiotic resistance in the pneumococcus bacterium globally are not for penicillins or macrolides, which usually require multiple DNA mutations or the import of foreign genes, respectively, but for sulfamethoxazole-trimethoprim, which can be selected from among a population of susceptible pneumococci by a single base change in the dihydrofolate reductase gene (Adrian and Klugman 1997). The direct selection of resistance following exposure of children carrying pneumococci has been shown in a prospective study in Malawi to occur in 42 percent of children exposed to sulfadoxine-pyremethamine for a week and in 38 percent of children a month after exposure to drug treatment for malaria (Feikin and others 2000).

Evolutionary biology suggests that drug selection pressure is an important factor in the emergence and spread of drug resistance. Although the relationship between antimicrobial use and drug resistance (in the pneumococcus, for example) is well established in developed countries (Bronzwaer and others 2002), direct evidence to support this hypothesis is less forthcoming in developing countries because of a lack of data on antibiotic use. Resistance to antimicrobials is less likely to arise in the poorest developing countries simply because of the lower levels of antibiotic use associated with poorer socioeconomic status. For instance, India—a large country with scant control over antibiotic prescribing—has very low rates of resistance among systemic isolates of pneumococci, at least in rural areas (INCLEN 1999). These low rates exist despite wide antibiotic availability, probably because extreme poverty limits the duration of antibiotic exposure for the treatment of acute pneumococcal infections. Rising incomes and increased affordability of antibiotics will likely change this low incidence of resistance; the same may be true of quinolones, which are widely available at relatively affordable prices, even in semirural and rural populations. This trend may be responsible for the emergence of nalidixic acid resistance to *Shigella* in Bangladesh and fluoroquinolone resistance to *Salmonella typhi* in India.

Recent evidence suggests that shorter courses of antibiotics may select for less resistance in the pneumococcus compared with longer courses (when patients comply with those courses) (Schrag and others 2001). Very low levels of resistance have also been found in isolated rural African communities (Mthwalo and others 1998). This observation, however, should not lead to complacency. Increased access to antibiotics in developing countries, without controls on over-the-counter use, has led to some of the highest rates of resistance in the world, as was seen with penicillin resistance in Vietnam. Relatively wealthy countries such as the Republic of Korea and Japan also have lax control and even greater access to funds to purchase antibiotics (Song and others 1999). Patterns of resistance differ by antimicrobial class, and resistance to several classes has been linked to particular patterns of use in developing countries. Macrolide use in children in China may be preferred to the use of beta-lactams, which are known to be associated in rare instances with serious anaphylactic reactions, and in Beijing and Shanghai, the highest global rates of macrolide resistance are encountered in nasopharyngeal isolates from children (Wang and others 1998; Yang, Zhang, and McGee 2001). Tetracycline use remains widespread in developing countries, and poor African countries, such as the Central African Republic, may have higher rates of resistance to tetracycline than to beta-lactams or macrolides (Rowe and others 2000).

The relationship between compliance and resistance emergence in the treatment of acute and largely self-limiting infections is less robust than in the case of chronic infections such as tuberculosis (TB). It is likely that resistance selection occurs more readily in the commensal flora (for example, the pneumococcal flora of the nasopharynx) than among the organisms causing the acute infection. Thus, shorter courses (and reduced compliance) may reduce the selection of resistance in commensal flora. In contrast, in TB, selection takes place in the infecting pathogen, and poor compliance is associated with the selection of resistant strains.

### Antibiotic Use in Animals

Many developed countries use antibiotics for veterinary uses, both for improving feed efficiency and rate of weight gain (subtherapeutic use) and for disease prevention and treatment (therapeutic use) (Levy 1992). Although the extent of antibiotic use in animals in developing countries is unknown, one study from Kenya reported that tetracyclines, sulfonamides, and aminoglycosides were the most commonly used antimicrobials for veterinary purposes (Mitema and others 2001). Over 90 percent of the antibiotics used were for therapeutic purposes, and there was no evidence of use for growth promotion.

There is strong evidence that the use of antibiotics in farm animals promotes the development of drug-resistant bacteria in animals (Aarestrup and others 2001). Because routes for the movement of these resistant bacteria to humans are available, there is sufficient circumstantial evidence that drug resistance in bacteria associated with food animals can influence the level of resistance in bacteria that cause human diseases (Wegener and others 1999). Furthermore, mathematical models indicate that the effect of subtherapeutic use on resistance in humans

is greatest when resistance levels are undetectable (Smith and others 2002). The appearance of drug-resistant strains of *Enterococcus faecium* in broiler meat products at retail outlets declined after the ban of antimicrobial growth promoters in Denmark (Emborg and others 2003). Salmonella has been recovered from chicken (35 percent), turkey (24 percent), and pork (16 percent) samples obtained from area supermarkets in Washington, D.C. (White and others 2001). There is evidence that dissemination of tetracycline-resistance-encoding plasmids between aquaculture and humans has already occurred in Europe (Rhodes and others 2000). The global nature of this problem became apparent in 2001, when authorities in some European countries found residues of chloramphenicol in tiger shrimp imported from China, Indonesia, and Vietnam (Holmstrom and others 2003).

### Transmission of Resistant Pathogens

Once resistance has emerged in a population, it can spread both geographically and between age groups. Unsafe drinking water, unsanitary conditions, and poor infection control in hospitals are risk factors for the transmission of all infections, including resistant ones. The transmission of resistant strains from children to adults has been suggested by anecdotal reports as far back as the 1980s (Klugman and others 1986). That association is strongly supported by the role of conjugate pneumococcal vaccine in reducing antimicrobial resistance among adult pneumococcal bacteremic isolates in the United States (Whitney and others 2003). The association of HIV infection with pediatric serotypes and antimicrobial resistance in pneumococci suggests the potential utility of this approach in reducing the burden of antimicrobial resistance in pneumococci in developing countries where the burden of disease is overwhelmingly associated with HIV infection in both children (Madhi and others 2000) and adults (Jones and others 1998).

### Disease Burden

Although no estimates of disease burden are currently available that are specific to drug resistance, the contribution of drug resistance to the burden of infectious diseases is believed to be large. Resistance has emerged in malaria, HIV, TB, and other bacterial infections that together constitute a significant proportion of the burden of disease in developing countries. An indication of the extent of the problem is provided by the burden of diseases for which drug resistance is a problem (table 55.1), as well as by the levels of drug resistance among these pathogens (table 55.2 and figures 55.1 and 55.2).

**Pneumococci.** Surveillance of drug resistance in pneumococci shows several general trends. The numbers of strains that are fully susceptible to penicillin-G, once nearly universal in most of the world, have declined by 30 to 50 percent in many countries and by 75 percent in some, as resistant clones have spread widely but irregularly throughout the world (Sa-Leao and others 2002). At the same time, percentages resistant to macrolides and to sulfamethoxazole-trimethoprim have increased, especially where those drugs have been widely used, and resistance to tetracycline or chloramphenicol has fluctuated widely. Linked resistance to these drugs results in a growing percentage of strains resistant to many or all of them. Resistance to fluoroquinolones is still rare but is beginning to be observed in many places (Ho and others 2001; Quale and others 2002).

Certain *Streptococcus pneumoniae* clones have been widely disseminated. A penicillin-, chloramphenicol-, and tetracycline-resistant clone (and sometimes erythromycin) of Spanish origin (Spain$^{23F}$-1) has, since its original description, been isolated in other parts of Europe, the United States, South and Central America, South Africa, and East Asia (McGee and others 2001). It is likely that this clone is even more widespread and that the absence of reports from other areas reflects the absence of molecular testing techniques needed to delineate

**Table 55.1** Estimated Burden of Disease in Disability-Adjusted Life Years, by Cause and Gender, 2001

| | Both sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| Condition | DALYs (Thousands) | Percentage of total | DALYs (Thousands) | Percentage of total | DALYs (Thousands) | Percentage of total |
| Infectious and parasitic diseases | 359,377 | 24.5 | 184,997 | 24.1 | 174,380 | 24.9 |
| Respiratory infections | 94,037 | 6.4 | 49,591 | 6.5 | 44,446 | 6.4 |
| Diarrheal diseases | 62,451 | 4.3 | 31,633 | 4.1 | 30,818 | 4.4 |
| Gonorrhea | 3,320 | 0.2 | 1,437 | 0.2 | 1,883 | 0.3 |
| Tuberculosis | 36,040 | 2.5 | 22,629 | 2.9 | 13,411 | 1.9 |
| Malaria | 42,280 | 2.9 | 20,024 | 2.6 | 22,256 | 3.2 |

*Source:* WHO 2002b, annex table 3, 194.

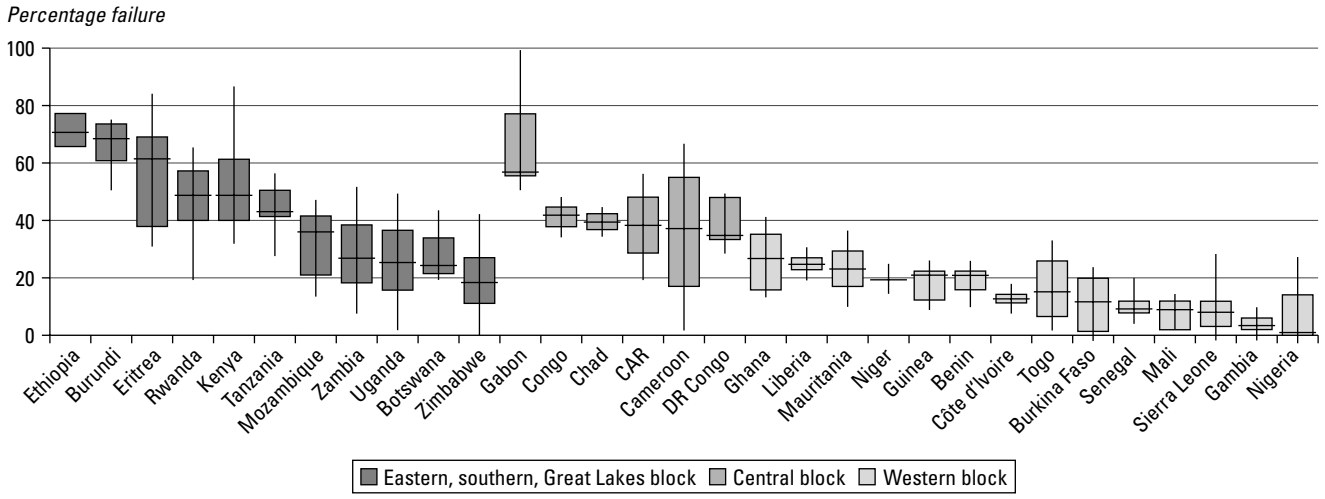
**Table 55.2** Prevalence of *S. pneumoniae* Not Susceptible to Three or More Drug Classes, Alexander Project 1998–2000

| Region and country | *N* | Percentage multiresistant defined as | | | |
|---|---|---|---|---|---|
| | | Any three drug classes excluding penicillin | Any three drug classes including penicillin | Any four drug classes | Any five or more drug classes |
| *Africa* | 540 | 14.3 | 24.8 | 13.5 | 3.3 |
| Kenya | 277 | 3.6 | 16.6 | 2.2 | 0.0 |
| South Africa | 263 | 25.5 | 33.5 | 25.5 | 6.8 |
| *Eastern Europe* | 1,109 | 10.1 | 11.7 | 6.0 | 1.0 |
| Czech Rep. | 275 | 0.7 | 1.1 | 0.4 | 0.0 |
| Poland | 453 | 13.0 | 15.2 | 6.4 | 1.1 |
| Russian Fed. | 161 | 10.6 | 12.4 | 3.7 | 1.2 |
| Slovak Rep. | 220 | 15.5 | 17.3 | 14.1 | 1.8 |
| *Western Europe* | 3,328 | 14.7 | 18.4 | 11.9 | 4.1 |
| Austria | 149 | 2.7 | 4.7 | 2.0 | 0.0 |
| Belgium | 230 | 13.9 | 15.7 | 7.0 | 2.6 |
| France | 444 | 35.6 | 49.1 | 34.9 | 11.7 |
| Germany | 321 | 4.7 | 5.9 | 1.6 | 0.0 |
| Greece | 431 | 18.6 | 19.5 | 13.9 | 2.1 |
| Italy | 304 | 19.7 | 22.4 | 9.9 | 1.0 |
| Netherlands | 185 | 0.0 | 1.1 | 0.0 | 0.0 |
| Portugal | 328 | 6.1 | 9.5 | 5.5 | 1.8 |
| Ireland | 54 | 9.3 | 14.8 | 9.3 | 1.9 |
| Spain | 295 | 27.8 | 32.9 | 25.4 | 15.3 |
| Switzerland | 349 | 5.7 | 7.7 | 4.9 | 2.3 |
| United Kingdom | 238 | 5.9 | 6.3 | 5.0 | 2.1 |
| *Far East* | 730 | 53.2 | 63.2 | 40.6 | 23.0 |
| Hong Kong, China | 193 | 76.2 | 79.3 | 70.5 | 60.1 |
| Japan | 404 | 48.3 | 63.1 | 29.2 | 6.4 |
| Singapore | 133 | 34.6 | 39.9 | 31.6 | 19.6 |
| *Middle East* | 314 | 11.2 | 18.2 | 10.5 | 4.1 |
| Israel | 148 | 8.8 | 12.2 | 8.8 | 2.0 |
| Saudi Arabia | 166 | 13.3 | 23.5 | 12.1 | 6.0 |
| *Latin America* | 2,861 | 13.3 | 20.1 | 12.1 | 1.9 |
| Brazil | 181 | 2.8 | 5.0 | 1.1 | 0.0 |
| Mexico | 248 | 21.0 | 31.1 | 20.2 | 3.2 |
| *United States* | 2,432 | 16.2 | 25.8 | 15.5 | 7.0 |
| All isolates | 8,882 | 17.5 | 23.7 | 14.6 | 5.9 |

*Source:* Jacobs and others 2003.
*Note:* Drug classes were defined as follows: β-lactams (penicillin MIC ≥ 0.12 mg/L), macrolides (erythromycin MIC ≥ 0.5 mg/L), tetracyclines (doxycycline MIC ≥ 0.5 mg/L), phenicols (chloramphenicol MIC ≥ 8 mg/L), folate pathway inhibitors (co-trimoxazole MICs ≥ 1 mg/L based on trimethoprim component), and quinolones (ofloxacin MIC ≥ 8 mg/L).

clones, rather than an absence of the organisms themselves. Other globally disseminated *S. pneumoniae* include specific clones of serotypes 19F, 14, 19A, 9N, 9V, 3, and 6 (McGee and others 2001). Spread of these pandemic clones has continued, even in areas where successful interventions have reduced selective pressure from antimicrobial use (Arason and others 2002). With increasing international travel, the potential of these strains to spread to areas where resistance is uncommon can no longer be considered remote.

**Shigella.** In many regions where *Shigella*, especially *Shigella dysenteriae*, is prevalent and an important cause of infant mortality, resistance first to sulfamethoxazole-trimethoprim, then to ampicillin, and commonly to tetracycline and

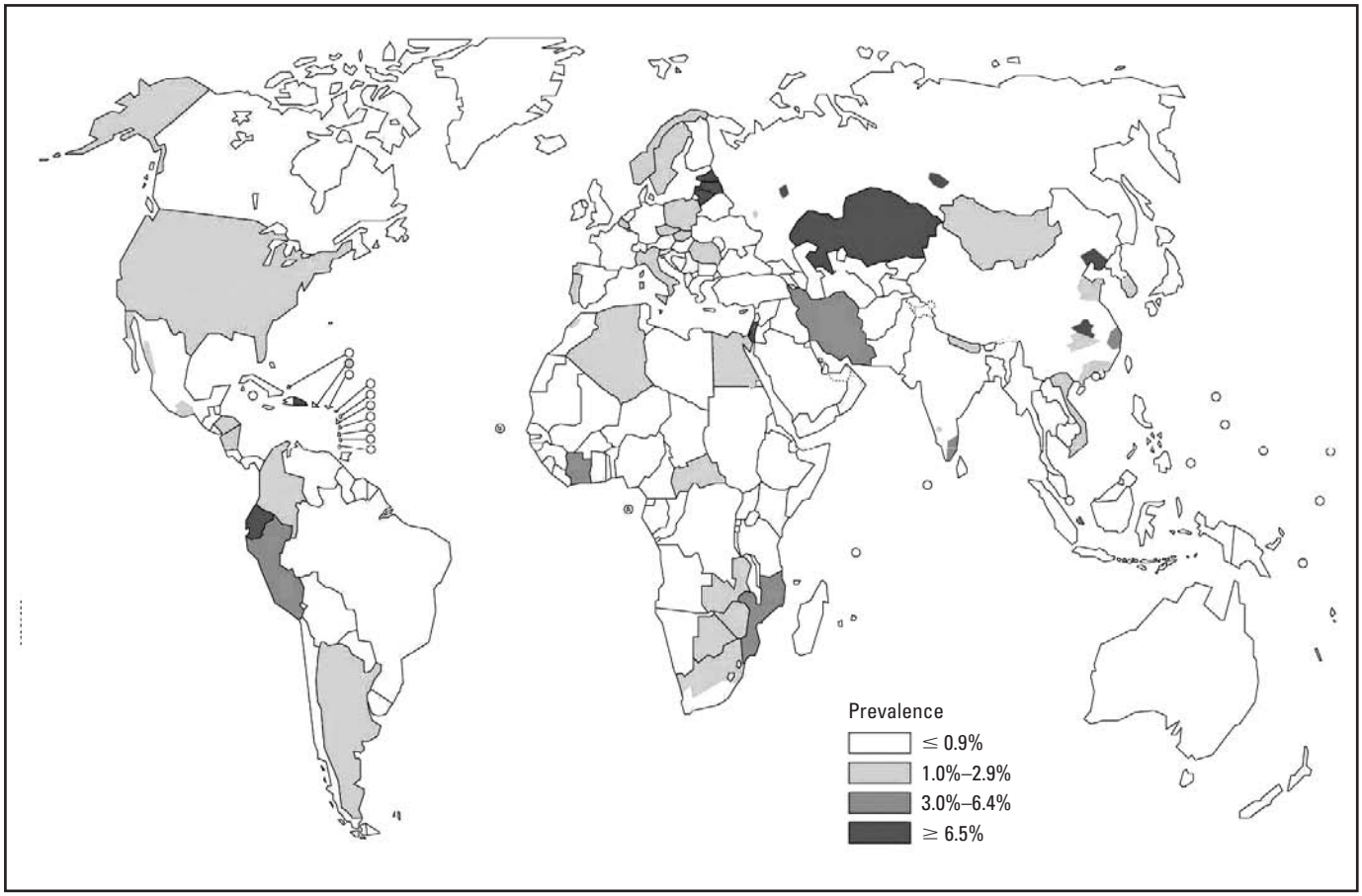



*Source:* WHO Regional Office for Africa, 1997–2002.

WHO has established 126 sentinel surveillance sites in 36 African countries that monitor the efficacy of locally used antimalarial drugs by following up patients in clinics. According to standard protocol (13, 14), results are expressed as I) early treatment failure (ETF); II) late clinical failure (LCF): in the future, late parasitological failure (LPF) will be considered as well. Treatment failure for policy change as shown here consists of the sum of ETF + LCF.

*Note:* The box indicates the 25th/75th percentile, the line limits lower/upper values, and where the lines cross, the median.

**Figure 55.1** Chloroquine Treatment Failure in Africa




*Source:* WHO-IUATLD 2004.

**Figure 55.2** Prevalence of MDR-TB among New TB Cases, 1994–2002

chloramphenicol has emerged and, over recent decades, spread to half or more of the strains sampled. In the 1990s, resistance has begun to emerge and spread to fluoroquinolones and third-generation cephalosporins, which in many places are the last effective oral drugs available (Ding and others 1999). In the past two decades, emergence and spread of *Shigella dysenteriae* type 1 resistant to sulfamethoxazole-trimethoprim, ampicillin, tetracycline, chloramphenicol, and—increasingly—nalidixic acid has reduced the effectiveness of these inexpensive and widely available antimicrobials in the empiric management of epidemic dysentery (Cunin and others 1999; Hoge and others 1995). The alternatives, ciprofloxacin and ceftriaxone, are relatively expensive and not always available. As a consequence, high fatality rates have been observed in a number of recent dysentery outbreaks (Legros and others 1998). The emergence of fluoroquinolone-resistant strains has quickly followed. The unchecked spread of these pathogens could pose a major public health challenge (Sarkar and others 1979).

**Gonorrhea.** Newly drug-resistant strains of gonococci tend to spread rapidly because of their peculiar epidemiology and the lack of control programs. Therefore, it is important to detect microepidemics of such strains, but this need is rarely met. The past half-century has witnessed the successive emergence and spread of gonococcal strains resistant to each new drug that becomes widely used to treat gonorrhea, including sulfonamides, penicillin, tetracycline, and sulfamethoxazole-trimethoprim (Tapsall 2002). Within less than a decade, such strains have commonly come to account for half or more of the isolates in many regions. The recent emergence of resistance to fluoroquinolones leaves only less available parenteral drugs, such as spectinomycin or ceftriaxone, as the reliable therapy (Ison and others 1998; Palmer, Leeming, and Turner 2001).

**Tuberculosis.** The emergence and spread of *multidrug-resistant tuberculosis,* which is defined as combined resistance to isoniazid and rifampicin, threaten the control of TB globally (Kochi, Vareldzis, and Styblo 1993). Patients infected with strains resistant to multiple drugs are very difficult to cure (Espinal and others 2000; Goble and others 1993), particularly if they are HIV-infected or malnourished (Fischl and others 1992), and alternative treatment is much more toxic and expensive (Drobniewski and Balabanova 2002). A patient with MDR-TB may remain infectious much longer than a patient with drug-susceptible organisms. Among new cases, prevalence of resistance to at least one TB drug ranges from 0 percent in some Western European countries to 57.1 percent in Kazakhstan, with a median of 10.2 percent. Multidrug resistance among untreated patients ranged from 0 percent in eight countries to 10.0 to 14.2 percent in six others. In previously treated cases, resistance to at least one drug ranged in different settings from 0 to 82.1 percent, with a median of 18.4 percent. Prevalence of MDR-TB in previously treated cases ranged from 0 to 58.3 percent, with a median of 7.0 percent (WHO 2004).

An estimated 273,000 (at a 95 percent confidence interval [CI]; 185,000 to 414,000) new cases of MDR-TB occurred worldwide in 2000. By simple extrapolation, 70 million people could be latently infected with MDR-TB, and more than 1 million active MDR-TB cases could remain among previously treated patients. Despite its threatening potential, MDR-TB is—and will probably remain—generally rare. Decades after the introduction of TB drugs, the global prevalence of MDR-TB in new patients remains less than 2 percent (Dye and Espinal 2001). Old animal studies (Cohn and others 1954) and recent analyses using molecular epidemiology (Garcia-Garcia and others 2000) suggest that MDR-TB strains might be, on average, less infectious. And unlike most other bacteria, *M. tuberculosis* replicates rather slowly (low mutation rate) and shares little if any genetic material. Thus, even in the absence of widespread treatment of MDR-TB, its prevalence may not necessarily explode (Kam and Yip 2001).

**Malaria.** Chloroquine-resistant strains of *Plasmodium falciparum* malaria appeared a half-century ago in Southeast Asia and South America and spread across Africa, especially East Africa, in the past quarter-century (Wellems and Plowe 2001). The use of molecular markers testing indicates the wide geographical reach of *pfcrt* polymorphism for chloroquine resistance, and *dhfr* and *dhps* polymorphisms for sulfadoxine-pyrimethamine. Current levels of treatment failure of chloroquine are in figure 55.1. There is evidence that malaria mortality, especially in children under the age of five, is rising as a consequence of increasing resistance to chloroquine (Greenberg and others 1989; Trape 2001). In response to increasing treatment failure, many countries, including Malawi, South Africa, and Tanzania, adopted sulfadoxine-pyrimethamine as first-line treatment; however, resistance to this drug too is growing in many parts of Africa. In Southeast Asia, the emergence of multidrug resistance to sulfadoxine-pyrimethamine and mefloquine over the past decade and a half has prompted the use of combination treatments that include artemisinin (Wongsrichanalai and others 2001).

## ECONOMIC BURDEN

Although few estimates have been made of the economic impact of drug resistance in developing countries, there is some indication that this burden is substantial. Estimates for costs associated with the loss of antibiotic effectiveness in outpatient prescriptions in the United States range from US$378 million to as high as US$18.6 billion (Elbasha 1999). A report by the Office of Technology Assessment to the U.S. Congress estimated the annual cost associated with antibiotic resistance in

hospitals (attributable to five classes of hospital-acquired infections from six antibiotic-resistant bacteria) to be at least US$1.3 billion in 1992 dollars (Office of Technology Assessment 1995). The U.S. Centers for Disease Control and Prevention (CDC) estimated that the cost of all hospital-acquired infections, including both antibiotic-resistant and antibiotic-susceptible strains, was US$4.5 billion.

Patients infected with resistant strains are more likely to be sicker, to be hospitalized for longer periods of time, and to die of the infection (Carmeli and others 2002). Both the duration of hospitalization and the attributable cost of treating methicillin-resistant *Staphylococcus aureus* were found to be nearly three time as large as those for a susceptible infection (Abramson and Sexton 1999). One problem with estimating the attributable morbidity and mortality that is caused by resistant pathogens is that patients who are infected with resistant strains are more likely to have been sicker in the first place. Therefore, the ability to appropriately control for the underlying severity of the illness that causes hospitalization is a concern.

Another important cost of resistance comes from the need to move to second-line treatments, which are often much more expensive than the first-line treatment that is no longer effective. For instance, treating the roughly 300 million cases of malaria with artemisinin-based combinations would involve an excess burden of roughly US$200 million each year in drug costs. Periodically changing first-line treatment may also involve costs of assessing alternate treatment regimens, retraining health care providers, and restocking health care facilities. Though all these impose a significant economic burden, especially in poorer countries, they may be an inevitable consequence of past drug use. A focus on the cost of resistance alone may be misleading, because it is potentially possible to eliminate drug resistance by not using any drugs. To appropriately assess the net benefits of drug use, one must include the cost of increased resistance and the benefits of antibiotic or antimalarial use in treating infections and preventing their spread to uninfected individuals.

## INTERVENTIONS

In this section, we discuss interventions to address the challenge of drug resistance (table 55.3). Many interventions to address the problem of resistance are the same as those that reduce the burden of disease (these are discussed in detail in the relevant disease-specific chapters in this volume). Reducing disease diminishes the need for drug treatment and, therefore, lowers the likelihood that resistant strains will emerge. Some interventions, such as the use of drug combinations, reduce the likelihood that resistance will emerge, whereas other interventions, such as improvements in drug prescribing and patient compliance with dosing, reduce the likelihood that a resistant pathogen will survive and proliferate. Prolonging the effective therapeutic life of existing drugs is not sufficient, however. Increasing incentives for pharmaceutical firms to bring new drugs to markets may also be called for.

### Drug Treatment Strategies

The appropriate choice of drug treatment is an important step in delaying the evolution of drug resistance. Drug combinations that include drugs with different targets were first used in the treatment of tuberculosis and have now become routine practice in the treatment of cancer and HIV/AIDS. Combinations of artemisinin and its derivatives with other antimalarials, notably mefloquine, have accelerated recoveries, increased cure rates, and reduced transmissibility. In the refugee camps on the western border of Thailand, where most of the recent studies with artemisinin combinations have been conducted, the use of combinations delayed the development of resistance and reduced the incidence of disease (Nosten and others 2000). The rationale behind drug combinations is that, if resistance results from spontaneous genetic mutations, the chance that a parasite will emerge that is simultaneously resistant to two drugs with unrelated modes of action (that is, drug targets) is the mathematical product of the individual parasite mutation frequencies multiplied by the total number of parasites exposed to the drugs (White 1998, 1999). Combinations, therefore, reduce enormously the probability that a resistant mutant will arise. Sequential deployment of the drugs is much less effective, because it does not exploit the multiplicative reduction in selection risk.

In the context of antibiotics, combinations have typically been used to broaden the spectrum of antimicrobial coverage rather than to reduce the likelihood of the emergence of resistance. With the development of new penicillins and cephalosporins with broader spectra of activity a decade ago, most serious infections have been treated with monotherapy. The use of combination therapy to preserve new classes of antibiotics from the emergence of resistance at a societal level may be rational, but it has not been implemented because of cost concerns and the potential for enhanced toxicity associated with the use of more agents than necessary to effect a cure in an individual patient.

Other strategies include periodic withdrawal of a drug or rotation between different drugs. These strategies depend on the extent of the fitness cost of resistance[1] and the extent of multidrug resistance, which may vary with the specific combination of pathogen and drug. Withdrawal or drastic decline in antimicrobial use is occasionally but not always accompanied by the replacement of resistant strains with sensitive ones. The effects of antimicrobial removal have best been assessed for antibacterial drugs in northern Europe, where drug use is

**Table 55.3** Potential Nonclinical Interventions: Evidence from Developing Countries

| Strategy | Intervention | Reference | Description | Study location |
|---|---|---|---|---|
| Treatment strategies | Combination therapy for malaria | Nosten and others 2000 | Use of an artesunate-mefloquine combination was found to reduce incidence of mefloquine resistance in *Plasmodium falciparum* malaria. | Thailand |
| | Cycling strategy | Kublin and others 2003 | Replacement of chloroquine with sulfadoxine-pyrimethamine resulted in a decline in chloroquine-resistant strains over an eight-year period to levels that permit reintroduction of the drug. | Malawi |
| | Drug heterogeneity | Bonhoeffer, Lipsitch, and Levin 1997; Laxminarayan and Weitzman 2002 | Modeling studies demonstrated the superiority and cost-effectiveness of policies involving use of different antibiotics on different patients compared with those using the same antibiotics on all patients. | n.a. |
| | Directly observed therapy short course | Balasubramanian, Oommen, and Samuel 2000 | Directly observed therapy reduced the probability of treatment failure. | Kerala, India |
| | | Dye and others 2002 | Directly observed therapy for TB was 2.8 times cheaper to deliver and between 2.4 and 4.2 times more effective than conventional treatment. | South Africa |
| Reducing selection pressure | Training providers | Bexell and others 1996 | Continuing education seminars for paramedical prescribers resulted in patients being prescribed antibiotics less frequently at intervention centers (34 percent) compared with control centers (42 percent). Drug choice and dosing were also improved. | Lusaka, Zambia |
| | | Santoso, Suryawati, and Prawaitasari 1996 | One-on-one educational interventions and seminars for medical and paramedical prescribers reduced antimicrobial prescription by 17 and 10 percent, respectively ($p < 0.001$). | Yogyakarta and Central Java provinces, Indonesia |
| | Training drug sellers | Agyepong and others 2002 | Training drug dispensers on patient communication resulted in modest improvements in the proportion of patients showing strict, full adherence to antimalarial regimen. | Dangme West District, Ghana |
| | Treatment guidelines with education | Qingjun and others 1998 | Blister packages increased compliance with chloroquine therapy to 97 percent, from 83 percent in the control group. | Hunan province, China |
| | Direct education of patients | Helitzer-Allen and others 1993 | Introduction of a nonbitter antimalarial tablet and a new educational message were effective in improving antimalarial prophylaxis compliance among pregnant women by 57 to 91 percent. | Malawi |
| | | Paredes and others 1996 | Video, radio, and printed bulletins were used to educate women in an intervention community on the management of watery infantile diarrhea. The overuse of nonindicated medicines (antibiotics and antidiarrheals) dropped 11 percent in the intervention group and only 7 percent in the control group. | Lima, Peru |
| Reducing spread of resistance pathogens | Hand washing | Kurlat and others 1998 | Training of nursing staff in hand washing, handling of infants, and care of intravenous lines resulted in 40 percent reduction in bacterimia rates. | Argentina |
| | Bednets (malaria) | Maxwell and others 2002 | Use of netting resulted in a 55 to 75 percent reduction in malaria morbidity and consequent conservation of antimalarial drug use. | Tanzania |
| | Vaccination | Klugman 2001 | Pneumococcal vaccines target the serotypes most commonly encountered clinically, which are more likely to be resistant to antimicrobials. | South Africa |

*Source:* Authors.

tightly regulated and susceptibility patterns are closely monitored (Seppala and others 1997). A recent study demonstrated that after chloroquine was replaced by sulfadoxine-pyrimethamine in Malawi because of a loss of effectiveness attributable to resistance, chloroquine-susceptible *Plasmodium falciparum* strains appear to have returned (Kublin and others 2003). Though the results of this study offer promise for stopping or reversing resistance trends, if antimicrobials are more sparingly and less indiscriminately applied, little is known about the rate at which the resistance to chloroquine may reemerge with widespread use of this drug.

Rotating between two or more antibiotics has been proposed to address the problem of nosocomial drug resistance in the United States (Bergstrom, Lipsitch, and McGowan 2000; McGowan 1986), even though there is not much supporting empirical evidence to date. In one hospital-based study, switching from gentamicin to other aminoglycosides reduced resistance to gentamicin. However, when gentamicin was reintroduced, resistance developed rapidly (Gerding 2000). Modeling studies have indicated that a superior strategy may be to increase antimicrobial heterogeneity so that different patients are treated with drugs to which mechanisms of resistance are independent (Bonhoeffer, Lipsitch, and Levin 1997; Laxminarayan and Weitzman 2002). Although this may be difficult to implement in many developing countries, the approach incorporates an evolutionary perspective that may help deal with drug resistance.

### Reducing Selection Pressure

Inappropriate antimicrobial use constitutes selective pressure without a corresponding benefit to individual or public health. (Eliminating all antibiotic use could, of course, eliminate the problem of drug resistance, but this strategy is clearly undesirable.) This multifaceted problem arises from behaviors of prescribers (not always physicians), dispensers (not always pharmacists), and consumers (not always infected). An important factor in overprescription is the issue of externalities; physicians, patients, and pharmacists have few incentives to consider the effects of their prescriptions or drug use on overall levels of resistance and the burden imposed on the rest of society. Physicians, both in private practice and in hospital settings, may also derive income from drugs sold and may, therefore, prescribe antibiotics more frequently than is desirable. In China, for instance, many hospitals rely on selling drugs for the bulk of their revenue (Hu and others 2001). Patient pressure demanding a prescription is known to influence prescribing in developed countries but could be less important in developing countries.

### Interventions at the Provider Level

In this section, we discuss interventions directed at health care providers and local retail pharmacies, such as education and professional accountability.

**Prescribing Patterns.** Studies in developing countries have shown that as much as a third of drug prescriptions, accounting for 20 to 50 percent of drug costs, are irrational and that antimicrobials are among the most frequently prescribed medications (Bosu and Ofori-Adjei 2000). Although altering prescribing behavior is an important intervention to control drug resistance, the widespread availability of drugs without a prescription limits its effectiveness. The prescribing problem may be worse among private practitioners than among public practitioners (Siddiqi and others 2002). Continuing education for practicing health workers is one type of intervention that has been tested in several countries. In the United States, a decline in antimicrobial prescribing in pediatric ambulatory care has been attributed to educational programs directed at physicians as well as the public (McCaig, Besser, and Hughes 2002). In developing countries, successful educational programs for prescribers have improved diagnostic quality, dispelled perceptions of patient pressure, reduced unjustified antimicrobial prescription (Chuc and others 2002; Hadiyono and others 1996), and reduced polypharmacy (Hadiyono and others 1996) among private as well as public providers, including nonphysicians (Chakraborty, D'Souza, and Northrup 2000; Chuc and others 2002). In general, these measurable outcomes were improved by 5 to 20 percent by a single intervention—a modest but significant change that is best combined with parallel interventions. Although cost-effectiveness was not a focus of the studies, the resultant reduction in drug use would ultimately result in cost savings. Important components of educational interventions are long-term commitment and refresher courses, and complementary interventions are also desirable (le Grand, Hogerzeil, and Haaijer-Ruskamp 1999).

Prescription guidelines, essential drug lists, and formularies are essential for defining policy and provide a useful framework on which educational interventions can be based (Laing, Hogerzeil, and Ross-Degnan 2001). The World Health Organization (WHO) recommends standard treatment guidelines as one of several approaches for promoting rational drug use. Also, guidelines proposed by pharmacy and therapeutics committees or external advisers have been applied in developing countries, with mixed results. Although standard treatment guidelines reduced antibiotic use for respiratory infections by 50 percent in Fiji (le Grand, Hogerzeil, and Haaijer-Ruskamp 1999), they did not alter prescription patterns in a Ugandan study and produced a detectable but insignificant effect in Sri Lanka (Angunawela, Diwan, and Tomson 1991). In general, follow-up was essential for success, and the use of standard treatment guidelines was more effective with nonphysician prescribers (le Grand, Hogerzeil, and Haaijer-Ruskamp 1999). Education must form part of any treatment guideline intervention, and evidence suggests that, if anything, educational programs are more effective than simply formulating guidelines (Laing, Hogerzeil, and Ross-Degnan 2001). Rigid guidelines

such as preprinted order forms or prepackaged drug kits for the management of community-acquired infections have been perceived as excessively prescriptive and have not been successful intervention tools (le Grand, Hogerzeil, and Haaijer-Ruskamp 1999). Devising incentives for compliance could potentially lower the higher prescription rates among private providers, where treatment guidelines by themselves are less likely to work.

Peer and supervisory monitoring increases professional accountability, thereby promoting the application of knowledge to practice. The requirement that antibiotic prescriptions for inpatients be countersigned by an infectious disease consultant was successful in reducing prescriptions by 50 percent, with a resultant cost savings of about US$350,000 over two years in a Panama hospital (Saez-Llorens and others 2000). Such a program would have limited applicability in other countries and settings where the number of trained medical professionals is small. A supervisory program in Vietnam, with medical equipment incentives, reduced the number of patients for whom antibiotics were prescribed and increased the number who received a correct dose regimen (Chalker 2001).

**Diagnostic Tests.** Bacterial culture and susceptibility testing, a necessary component of rational antimicrobial prescribing, is uncommon in many developing countries (Okeke, Lamikanra, and Edelman 1999). Furthermore, diagnostic tests to confirm or refute infections are also commonly unavailable or unreliable, so diagnoses are made largely on the strength of clinical signs and symptoms (Berkley and others 2001). Laboratory tests are expensive and routinely cost more than an empiric drug that could be effective. In contrast, malaria dipsticks can be an inexpensive tool for case detection and may be cost-effective in low transmission settings (Rimon and others 2003). Clinicians have been known to use chemotherapy as a diagnostic tool: a cure would confirm a diagnosis. Susceptibility testing of at least some specimens will provide much-needed surveillance data to support empiric prescribing, although efforts should be made to take into account spatial heterogeneity in resistance patterns.

**Retail Pharmacies and Outlets.** Drug distributors, including not only pharmacists but also pharmacy attendants, patent medicine stallkeepers, and itinerant drug sellers, often sell drugs without prescription and are an important source of primary care for people in many developing countries (Igun 1994; Indalo 1997). Patients in search of convenient and accessible health care often seek treatment at drug retail premises. Many drug sellers have not been formally trained in diagnosis and prescription but often have financial incentive to perform those tasks, with varying degrees of competence. Despite the potential loss of business to storekeepers, educational interventions have been successful in increasing prescription requirement demands and promoting referral advice, all steps in the right direction (Chuc and others 2002). Models for delivering educational interventions in developing countries vary but can be broadly classified into focus group discussions (Hadiyono and others 1996) and large seminars (Bexell and others 1996). Both models have been found to be of comparable effectiveness; however, applicability and cost are situation-specific (Santoso, Suryawati, and Prawaitasari 1996).

**Drug Quality.** Ensuring drug quality is important, both to benefit the individual patient and to ensure that a patient is not subjected to suboptimal doses that would promote drug resistance. The few studies that have been conducted indicate that more than half of the antimicrobials marketed in developing countries do not match their labels. Hence, even when prescribers and consumers are using the drugs responsibly, therapeutic failure and subinhibitory levels of antimicrobials may occur. Substandard drugs are those that are degraded as a result of expiration or improper storage or that are counterfeit (Okeke and Lamikanra 2001; Prazuck and others 2002; Taylor and others 2001).

### Interventions at the Patient Level

Improving communication between patients and providers could improve adherence to prescribed antimalarial regimens (Agyepong and others 2002). Compliance can also be positively affected by packaging. Blister packages, when combined with proper instruction about drug use, have been shown to produce modest increases in antimalarial compliance, particularly for long-term regimens, such as with primaquine (Qingjun and others 1998). Blister packages are also time-savers for primary health care workers, potentially allowing them more time to advise patients on drug use. However, the introduction of blister packages must be accompanied by clear directions to avoid injury following ingestion of blister packages.

Reducing patient self-medication may also desirable, although the effect on drug resistance remains to be precisely quantified. Enforcement of prescription-only regulations for most antimicrobials reduces self-medication in developed countries (Carey and Cryan 2003; Goff, Koff, and Geiling 2002; Pechere 2001) and may be desirable in developing countries as well. However, such a strategy may be difficult to implement in developing countries. There have been only rare reports of reduction in antibiotic use following blanket enforcement of prescription supply legislation in areas where antibiotics are freely available (Bavestrello, Cabello, and Casanova 2002). Opponents to enforcement demand a heavy financial and political investment, implying that a black market for medicines could emerge, particularly if the demand for these drugs is not lowered (Bhutta and Balchin 1996; le Grand, Hogerzeil, and Haaijer-Ruskamp 1999). The sale of antimicrobials is a lucrative business, even when illegal, because of high demand.

Educational interventions directed at consumers have been proposed to reduce self-medication and increase compliance, but evidence for the effectiveness of this strategy remains inconclusive, largely because so few studies have been conducted. Gonzalez Ochoa and others (1996) demonstrated that, although refresher training for health personnel managing acute respiratory infections reduced antibiotic prescribing by 9 to 19 percent in two intervention areas in Havana, no benefit was seen from community education programs when used alone or in conjunction with prescriber training. In contrast, Denis (1998) was able to show that a poster had 5 percent effectiveness alone and 20 percent effectiveness when used with a video to promote appropriate use of quinine and tetracycline regimens for malaria among Cambodian villagers. The best method to deliver information about the consequences of antibiotic resistance remains to be identified and will need to be modified to suit different cultures (Marin and others 1995).

In the case of tuberculosis, first-line directly observed therapy (DOT) remains one of the most cost-effective of all public health strategies (WHO 1994). The discovery that DOT can be administered successfully as a short course (DOTS) has been pivotal to successful implementation. Relatively simple, the DOTS approach can improve patient compliance, cure the vast majority of new TB patients, and prevent transmission of the disease and the emergence of MDR-TB (Balasubramanian, Oommen, and Samuel 2000; Dye and others 2002). Unfortunately, many countries have been slow to adopt and implement DOTS programs correctly, and only a minority of TB patients worldwide are managed according to this protocol (Dye and others 2002; Pungrassami and others 2002). Because many patients either are treated outside the DOTS regimen or do not adhere to the long-term chemotherapy necessary to eradicate the causative organism, MDR-TB is likely to emerge and treatment costs are likely to escalate to as high as 1,000 times the cost of conventional treatment of drug-sensitive infection.

A DOTS program requires good laboratory support for case identification and is highly employee intense, requiring health workers to observe the ingestion of every dose of antimicrobials over several months. However, the potential economic gains are immense because of the high costs of allowing the continued spread of the disease and of managing resistant patients and because of the benefit of reduced hospital admissions (Dye and others 2003). Several studies have investigated means for reducing the cost of conventional DOTS programs without compromising effectiveness. Lwilla and others (2003) demonstrated that both institutional and community-based DOTS programs are effective, permitting cost-effective implementation in remote areas. Furthermore, although DOTS involves supervised drug dosing, highly trained health workers are not essential. Studies in South Africa, Haiti, and Thailand have found that DOTS was effective when drug administration was supervised by appropriately trained volunteers, including storekeepers and former TB patients (Barker, Millard, and Nthangeni 2002; Pungrassami and Chongsuvivatwong 2002).

Although DOTS was not designed to cure patients with MDR-TB, it succeeds in 50 percent of cases (Espinal and others 2000). Controversy has emerged about the best approach to MDR-TB in resource-constrained settings. Although some experts assert that standard TB control prevents the emergence of MDR-TB in a cost-effective way (Chaulet, Raviglione, and Bustreo 1996) and that expensive treatment of MDR-TB would divert scarce resources from struggling DOTS programs, others argue that it is unethical to abandon MDR-TB patients and maintain that, if untreated, MDR-TB strains will become dominant, undermining tuberculosis control in future generations (Farmer, Becerra, and Kim 1999). These arguments are of particular consequence for programs in poor countries.

### Application of Antibiotics for Nonhumans

The use of antimicrobial agents in agriculture and aquaculture can contribute to the spread of antimicrobial resistance in humans, although the extent of this contribution has not been precisely quantified. It is believed that agricultural antibiotic use hastens the emergence of resistant pathogens in humans, and antibiotic use in humans contributes to the spread of resistance once it has emerged (Smith and others 2002). There are no reliable estimates of the extent to which antibiotics are being used for such nonhuman purposes even in developed countries. In developing countries, one would expect use to increase with rising incomes and greater industrialization of agriculture and food production.

WHO has recommended that antimicrobials normally prescribed for humans should no longer be used to promote growth in animals (WHO 2000). Some countries in Europe, including Denmark and Sweden, have already phased out such use, and under the current plan, the European Union will ban the use of antibiotics for growth promotion by 2006. Evidence of the effect of a ban on antibiotic use in swine production is available from Denmark. Although the ban significantly lowered the use of antibiotics in growth promotion and raised the cost of swine production by less than 1 percent, the resulting higher incidence of disease among swine increased the use of antibiotics used for veterinary therapeutic purposes (Hayes and Jensen 2003). A similar increase was noted in Sweden, where antibiotic use in animals was banned in 1986; however, this problem was temporary, and in the longer term, livestock producers were able to move to an effective production system with lower antibiotic use (Wierup 2001).

### Containing the Spread of Resistant Micro-organisms

Although selection is a necessary component of the resistance archetype, the dissemination of resistant organisms may have a far greater effect on the current situation (Zaidi and others 2003).

Interventions that block this dissemination have the added benefit of improving health by interrupting disease transmission and reducing the need for antibiotics in the first place. A case in point is the reduction in drug-resistant *Streptococcus pneumoniae* infections in the United States following the introduction of a multivalent vaccine that protected against the serovars with which resistance is commonly associated (Whitney and others 2003). By contrast, a drop in antibiotic use had no detectable effect on resistance within a short period (Arason and others 2002). Because these types of interventions are easier to evaluate, and in many cases are cheaper to implement (Coast and others 2002), they are likely to be of great value to public health in developing countries.

Interventions that interfere with the spread of many infectious diseases will have a parallel effect on the dissemination of resistant micro-organisms. Because the potential health benefits are obvious, these types of interventions are likely to be sustained (Wilson and Chandler 1993). A simple, cost-effective example is hand washing, which could reduce diarrhea by 47 percent while also having beneficial effects on acute respiratory tract and other community-acquired infections (Curtis and Cairncross 2003) (see chapters 19 and 35). Similarly, insecticide-impregnated bednets are another important intervention for the control of malaria (see chapter 21).

The emergence, persistence, and intra- and interhospital spread of multidrug-resistant organisms have all been facilitated by inadequate infection control practices. Furthermore, the emergence and spread of drug-resistant nosocomial pathogens from hospitals to the community are also a concern, and a history of hospitalization has been identified as a significant risk factor for the acquisition of a resistant infection in family members (OR 4.5, $p = 0.007$) (Zaidi and others 2003). Unfortunately, we lack good clinical trials that compare the different approaches to infection control programs and their ability to control antimicrobial resistance in hospitals and other health care facilities (Duse and Smego 1999). It seems reasonable to assume, however, that if the overall frequency of nosocomial infections is decreased in a health care facility, then the need for antimicrobial agents may be reduced. Furthermore, well-structured and rational infection control strategies that balance resources with the magnitude of the local problem must surely play an important role in decreasing morbidity, mortality, and costs (direct and indirect) to the patient, his or her family, the hospital, and the health care sector in general. Hospital-acquired infections rank among the most important causes of death, either directly or indirectly, in the developing world (Duse and Smego 1999; Ponce-de-Leon and Rangel-Frausto 1993).

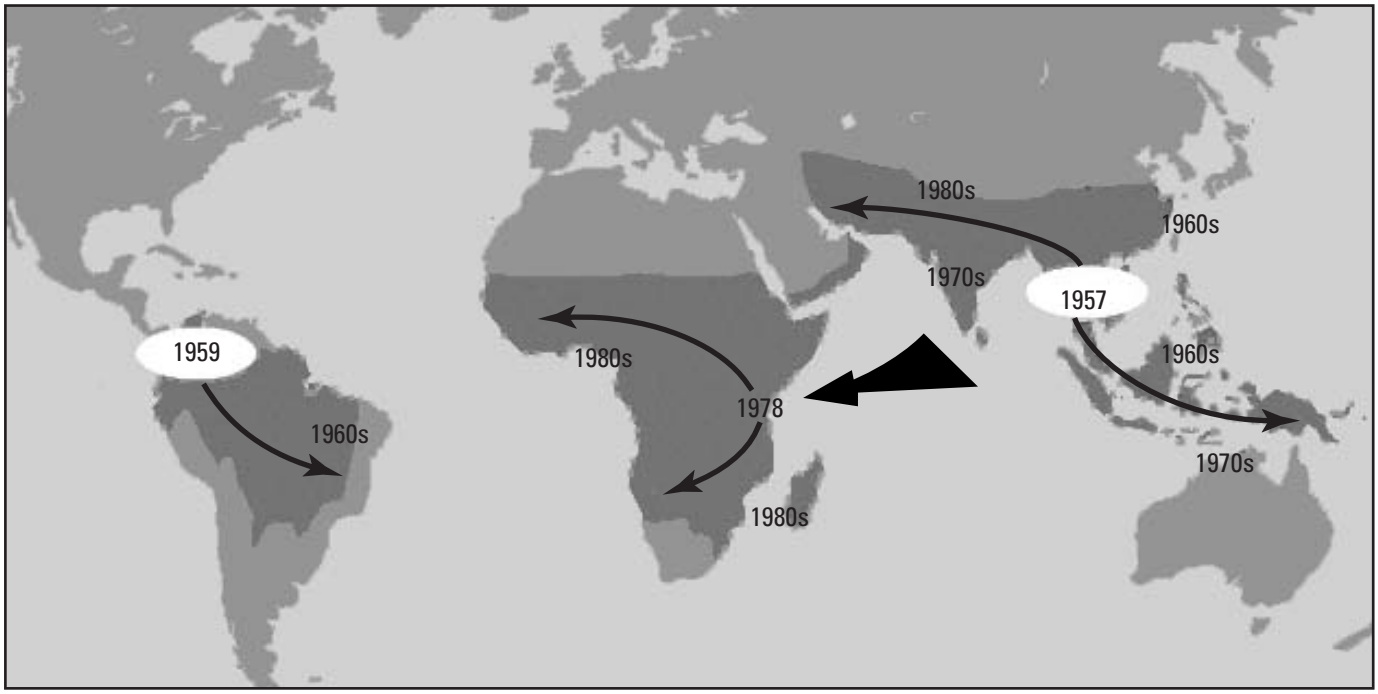
### Global Coordination

Antimicrobial resistance is a global challenge that requires urgent global action, not just across national boundaries but also across the whole range of sectors involved. International travel and trade, particularly of food products, have facilitated the rapid globalization of resistance, and actions undertaken by any single nation have consequences for other countries. Drug resistance may threaten health gains made in other spheres of public health. Thus, coinfection with antimicrobial-resistant pathogens and HIV can lead to more rapid disease progression and enhanced dissemination of resistant pathogens. The emergence of antimicrobial resistance is considered a major threat to the future security and political stability of some regions (CIA 1999). Figure 55.3 shows the likely geography of the emergence, spread, and evolution of chloroquine resistance.

Concerted international action is needed to contain antimicrobial resistance. Failure of individual countries to act to contain resistance could lead to both national and international consequences. For instance, the use of artemisinin as monotherapy in any single country could potentially lead to the rapid evolution of resistant strains, which could threaten the use of this valuable drug in any other part of the world.

There is a considerable need for greater international collaboration on surveillance of antimicrobial resistance, both for routine surveillance and as an early warning system for unusual resistance events. Although existing laws at the international level require reporting of some infectious diseases, they do not include any systematic reporting of antimicrobial resistance. Certain multiresistant pathogens, such as methicillin-resistant *S. aureus,* are now notifiable at the national level in some countries, but the global nature of the resistance problem means that national legal measures alone are not enough. At the same time, the creation of new international duties would be undermined if they were not incorporated into national law (Fidler 1998).

To support such surveillance, the World Health Organization makes software (WHONET) available to enable clinical laboratories to enter their drug susceptibility test results into databases that can be analyzed for local management of resistance. Those results can also be merged, creating, thus far, approximately 80 national surveillance databases. Statutory notification about pathogens with new resistance phenotypes is under active discussion in several countries. Interpretation of existing surveillance data is hampered by the multiplicity of methods used to measure resistance and by the difficulties of assessing the quality of the data. Enhanced laboratory capacity is needed in many countries to provide effective diagnostic services and resistance surveillance. Multicountry external quality assurance schemes already exist but need to be extended to cover more resource-poor nations. WHO has begun establishing international surveillance standards by issuing antimicrobial resistance surveillance standards (WHO 2002a), guidelines for the management of drug-resistant tuberculosis (WHO 1997), and protocols for detection of antimicrobial drug resistance (WHO 1996). Monitoring the use of antimicrobial agents




*Source: Cell* 1997.

**Figure 55.3** Global Spread of Chloroquine-Resistant Strains of *P. falciparum*

is an important aspect of surveillance and needs to be strengthened internationally.

Coordinated surveillance for drug resistance to TB may be a useful prototype to follow. By 2003, a global network of 20 supranational reference laboratories and five regional subnetworks, known as the World Health Organization–International Union against Tuberculosis and Lung Disease (WHO–IUATLD) Global Project, was reporting data on representative cases of TB from 62 countries. The network has monitored participants' laboratory testing methods and developed uniform definitions, such as establishing clinical categories for new cases and previously treated cases. The WHO–IUATLD Global Project, which covers approximately 33 percent of the world's population and 28 percent of its reported cases of TB, and other surveillance efforts reveal great variations from place to place in the prevalence of resistance to antituberculosis drugs.

The WHO Global Strategy for Containment of Antimicrobial Resistance (WHO 2001) recommends more than 60 interventions that can slow the emergence and reduce the spread of resistance in diverse settings, and it provides a blueprint for global coordinated action. A recent report by the Institute of Medicine calls for such coordinated action at a global level to subsidize artemisinin-based combination treatments for malaria for deployment in developing countries to ensure that combination treatments are available at the same or lower price than monotherapies. The underlying rationale is that this strategy would both save lives in the short term and delay the emergence of resistance in the long term, thereby benefiting all malarious countries (Arrow, Panosian, and Gelband 2004).

### Encouraging the Development of New Drugs

The development of new products has not kept pace with the problem of addressing microbial resistance to drugs that are used to treat infections in human and veterinary medicine. In the context of drug resistance, it is not sufficient to design policies that will encourage only the development of new drugs. It is also important that such policies give pharmaceutical firms (a) an incentive to invest in new classes of drugs, rather than products that belong to existing drug classes and that are, therefore, more likely to be rendered obsolete by resistance, and (b) an incentive to care about drug resistance when making decisions about how to market and sell their product. (See chapter 6 for a discussion of product development not specific to drug resistance.)

Current public and private investment in drugs, vaccines, and other products to control major infectious diseases in developing countries has recently been less than 2 percent of total health research expenditures throughout the world. Of the 1,393 new chemical entities registered by Western health authorities between 1975 and 1999, only 13 (less than 1 percent)

were intended for the treatment of tropical diseases, and half of those came from veterinary research.

Evidence suggests that in recent years, a steadily decreasing proportion of pharmaceutical company profits has been invested in antimicrobial research and development (R&D). One reason given for this decline is increased development costs, which result from more complex clinical trials, longer development times, and the relative attractiveness of returns from investing in drugs for chronic diseases, which must be taken continuously rather than just for the duration of an infection. Efforts to reduce inappropriate antibiotic use may paradoxically also reduce incentives for pharmaceutical firms to invest in developing new products (Monnet and Sorensen 2001; Philipson and Mechoulan 2003). The related issue, of using shorter treatment courses for many infections, may also affect R&D incentives (Pichichero and Cohen 1997).

Encouraging research into antimicrobial agents that will be used primarily in low-resource countries poses particular challenges, given the need for drug companies to make a profit. Various incentives to the industry, including both push and pull mechanisms, have been discussed (Kettler 2000). *Push mechanisms* consist of incentives to offset R&D costs, such as research grants, tax credits, public investment in applied research, cost-sharing between companies, and establishment of local development facilities. *Pull mechanisms* are designed to create a market, thereby improving the likelihood of a return on investments. They could include an international purchase fund for a new antimicrobial that meets specific criteria (United Kingdom Government 2001), tax credits on sales, and favorable patent policies, such as extension of patent terms or market exclusivity on new products. Time-limited exclusivities on new, clinically useful formulations might stimulate the additional pharmaceutical and clinical studies that are needed to support licensure. Better patent protection for new antimicrobial agents in areas of the world where patent laws are not enforced today would also help.

Patent policies to encourage investment in developing new antibiotics should also take into consideration the effect of those policies on incentives that would encourage pharmaceutical firms to conserve the effectiveness of their products. If effective patent lengths are too short, pharmaceutical companies will be less likely to care about growing drug resistance to their product and will be more interested in maximizing sales of their products during the period of patent production. Extending patent lengths may not solve the problem, however. If different firms make closely related antibiotics that have linked mechanisms of action, no single firm may have an incentive to care about drug resistance (Laxminarayan 2002). Increasing patent breadth, one solution to this problem, would have the added advantage of creating an incentive for firms to invest in developing new classes of drugs rather than introducing drugs that are closely related to existing products in modes of action.

## IMPLEMENTATION OF STRATEGIES: TWO LESSONS FROM EXPERIENCE

### Integrated Management of Childhood Illness

The program on the integrated management of infant and childhood illness (IMCI) was initiated by WHO, the United Nations Children's Fund, and other technical partners. The program, which provides a framework for stepwise assessment and management of sick children, has been successful in averting unnecessary antibiotic and antimalarial use and in reducing the cost of medications (Gove 1997). An underlying objective of IMCI is to detect, where present, conditions other than those responsible for the primary complaint. The result is that rational prescribing may actually increase, but because IMCI guidelines reduce irrational prescribing, the net effect is a reduction in drug use, including antimicrobials (Oluwole, Mason, and Costello 2000). Drug costs associated with treating children in Kenya were found to be reduced from an average of 44 cents per patient (U.S. currency) to between 16 and 39 cents per patient when IMCI guidelines were followed (Boulanger, Lee, and Odhacha 1999). A study that compared prescriptions arising from standard and IMCI-guided consultation with a health worker in Kaduna state, Nigeria, found a reduction in polypharmacy when IMCI guidelines were used, from a median of five drugs down to two drugs, and an 80 percent reduction in the cost of all medicines (Wammanda, Ejembi, and Iorliam 2003). This reduction represented savings of 93.4 and 68.6 percent for antibacterials and antimalarials, respectively, although part of the savings could be attributed to the substitution of tablets for more expensive syrup formulations.

The contribution of IMCI to promoting judicious drug use is worth noting. A study that compared four districts of Kenya—two districts that had IMCI programs (Morogoro and Rufiji) and two that did not (Ulanga and Kilombero)—found that in 73 percent (95 percent CI; 65–80) of consultations studied in the IMCI intervention districts, a child needing an oral antibiotic or antimalarial was prescribed correctly, compared with 35 percent (95 percent CI; 25–45) in the control districts (Armstrong Schellenberg and others 2004). Also, in the IMCI districts, 86 percent (95 percent CI; 80–92) of children who did not need antibiotics left the facility without an antibiotic, compared with 57 percent (95 percent CI; 48–66) in the control district.

### Directly Observed Therapy

Strict compliance and cure verification make it possible to conduct directly observed therapy using shorter-term regimens (the DOTS program). Outpatient treatment of a single TB case in Pakistan, with complete compliance, was recently estimated at US$164 and increased to US$310 when an institution-based DOTS program was applied (Khan and others 2002). In Beijing, the cost of saving one disability-adjusted life year

(DALY) is 10 times higher when a DOTS TB program is not used (Xu, Jin, and Zhang 2000). Recent expansion of DOTS care in India has resulted in savings of about 0.2 million lives and US$400 million in indirect costs (Khatri and Frieden 2002). Progress with DOTS in India was initially slow, but following better implementation, recent findings suggest that huge successes have been made in the past five years. The successes can largely be attributed to improved management of the program, area-specific appraisals, infrastructure, personnel, and technical support as well as continuous supervision (Khatri and Frieden 2002). This model is one that may apply in other developing countries.

In New York city, individualized chemotherapy based on drug susceptibility testing was nearly as effective in new patients with MDR-TB as in those with drug-susceptible TB (Telzak and others 1995), and the number of MDR-TB cases decreased by more than 90 percent within the decade (Fujiwara and others 1997). The relatively large number of MDR-TB cases in high-income countries made second-line drugs more available and affordable, and experience in the management of MDR-TB grew considerably over the past decade (Mukherjee and others 2004). Yet questions remained about which interventions had led to the city's success. In 1999, WHO created a working group on DOTS-plus to assess the feasibility and cost-effectiveness of treating MDR-TB in low- and middle-income countries (Espinal and others 1999). DOTS-plus has already negotiated a 90 percent price reduction from the pharmaceutical industry (Gupta and others 2001), and experience from Peru suggests feasibility and a mean cost of US$211 per DALY gained (Suarez and others 2002).

## AGENDA FOR ACTION

Although the evolution of resistance is a biological phenomenon, it is influenced strongly by the behavior of physicians, patients, and hospital administrators. In the language of economics, drug resistance is an *externality* associated with the use of antibiotics—a consequence not taken into consideration by those who use antibiotics or antimalarials. From a public policy perspective, there may be an economic case for societal intervention, because patients, physicians, and nations acting on self-interest alone may produce a higher degree of drug resistance than is ideal for society as a whole. From a global perspective, there is a case for international coordination to ensure that the actions of any single country or region do not increase the likelihood of emergence of resistance, which could then spread to other parts of the world.

Rising incomes in the developing world are likely to encourage greater use of Western medicine and, consequently, greater use of antibiotics. Moreover, the adoption of government-sponsored or employer-sponsored insurance plans in many parts of the developing world could further increase drug use. Because developing countries will be less able to bear the costs of increasing resistance, it is important that the patterns of overuse and misuse observed in high-income countries not be repeated. The right financial incentives must be in place for both patients and physicians to face the full cost of using antibiotics and antimalarials and to ensure that these drugs are not overused.

### Recommended Interventions

Sets of interventions specific to the diseases discussed in this chapter are described below.

**Pneumococci.** A number of affordable interventions can be considered. Data suggest that hand washing can interrupt not only the spread of pathogens causing diarrhea but also the transmission of nosocomial pathogens, and it can reduce respiratory infection–related mortality and morbidity. The promotion of a culture of hand washing requires access to clean, sufficient water—an urgent goal. Patient education to reduce demand for antibiotics for viral infections, and alteration of perverse incentives for physicians to prescribe antibiotics excessively are recommended. Pneumococcal conjugate vaccine has been shown to reduce the burden of antibiotic-resistant invasive disease, reduce transmission of resistant strains, and reduce antibiotic use in vaccine recipients and their siblings. Strategies for introducing this type of vaccine into the high-risk populations of developing countries are urgently needed. Better diagnostics are a key to more appropriate and focused prescribing, but their application is likely to be delayed in poor countries. The long-term effects of blanket recommendations for antimicrobial prophylaxis among HIV-infected populations must be closely monitored.

**Shigella.** Interventions must include improved strategies for case definition, clinical recognition, and appropriate therapy of dysentery. These strategies require a focus on educating physicians and caregivers as well as restrictions on over-the-counter availability of antibiotics in developing countries. Recent strategies for reducing antimicrobial prescribing for diarrhea at the community level also include coadministration of zinc with oral rehydration therapy. This strategy has been shown to lead to significant reduction in antimicrobial prescribing for diarrhea in Bangladesh and may be a useful adjunctive strategy (Baqui and others 2002).

**Tuberculosis.** The top priority must be the expansion of DOTS (Iseman, Cohn, and Sbarbaro 1993), which itself can prevent the emergence of MDR-TB (Dye and others 2002). In individual countries or parts of countries, however, additional strategies may be appropriate. Pablos-Méndez, Gowda, and Frieden

(2002) have grouped countries according to the proportion of TB patients completing treatment successfully and the level of MDR-TB among previously untreated patients. The resulting matrix provides a reasonable framework for deciding whether to use second-line drugs in a national program. Countries with treatment success of less than 70 percent should introduce or improve the DOTS strategy as the top priority. In settings with primary MDR-TB of less than 1.5 percent, treating MDR-TB is not a public health priority, although individual cases could be referred to clinical experts. The hotspots—those areas with primary MDR levels above 5 percent—are international public health emergencies. Infection control practices must be emphasized in such settings. Intermediate situations are ideal for additional research comparing DOTS with various individualized regimens against MDR-TB.

**Malaria.** With declining effectiveness of chloroquine and rapidly emerging resistance to its replacement, sulfadoxine-pyrimethamine, it is imperative that significant attention be paid not just to the choice of an appropriate first-line treatment for malaria, but also to strategies to prolong the effective therapeutic life of the new treatment. WHO has recommended that new artemisinin derivatives be used only in combinations with other drugs. There is evidence that artemisinin has already found its way into shops as monotherapy; discouraging the use of this valuable drug in monotherapy through public subsidies for combinations, by mandate, or through a combination of measures is a necessary first step. Discouraging the use of artemisinin as monotherapy is not sufficient, however. It is also important to ensure that the partner drug in the combination used with the artemisinin derivative is effective and, hence, able to protect the artemisinin. Therefore, discouraging the use of the partner drug as monotherapy, except in cases in which no safe alternative exists, such as for sulfadoxine-pyrimethamine in intermittent preventive treatment of malaria in pregnant women, is an important step in ensuring the long-term sustainability of malaria treatment. Training shopkeepers and other purveyors of antimalarial treatments to recognize symptoms of malaria and to use diagnostics to detect malaria would help reduce malaria treatment to instances for which it is appropriate and would reduce the likelihood of the emergence of resistance. Finally, steps to reduce the burden of malaria through the use of insecticide-treated bednets and, in some areas, residual household spraying would help reduce the need for antimalarial treatment and thereby reduce treatment selection pressure.

### Research Agenda

A description of a research agenda to explain the full range of issues related to drug resistance is outside the scope of this chapter and has been accomplished by other groups. Here, we restrict our focus to the following five priorities:

- accounting for attributable morbidity and mortality and the economic burden of drug resistance in the developing world
- measuring the cost-effectiveness of interventions to improve prescribing and patient compliance
- researching incentives for firms to invest both in developing new drugs and in maintaining the effectiveness of existing drugs
- identifying socioeconomic, demographic, and cultural factors that determine antibiotic use and misuse and projecting how antibiotic use will change in future years
- designing international coordinating mechanisms for surveillance to report resistance outbreaks and coordinate strategies for appropriate drug use, recognizing the global nature of drug resistance.

## CONCLUSION

Modern medicine rests on the bedrock of effective anti-infective drugs. Unfortunately, the use of drugs creates selective pressure for resistance to arise, and thus, the growth of resistance may be an unavoidable consequence of our actions in treating disease. It is, however, important for governments to intervene to ensure that the effectiveness of our current arsenal of anti-infectives is not depleted at an excessively rapid rate. Given the potential for international spillovers of resistant pathogens and the ability of actions taken in one region or nation to affect other parts of the world where a disease is prevalent, a strong case can be made for coordinated international action—similar to another urgent global situation, the depletion of the ozone layer and the subsequent Montreal Protocol to phase out the use of chlorofluorocarbons—to manage the evolution of resistance.

Some interventions that we recommend, such as more restrictive prescribing policies and the use of combinations, could, in the absence of subsidies from the state, place a burden on the poorest patients. For instance, an overly restrictive policy on drug sales at the retail level could harm those who have less access to formal medical care and prescriptions. There may be similar effects from mandating that antimalarial drugs be sold in combinations that the poor cannot afford. Efforts to manage resistance should not be balanced on the backs of the poor, however, because the rationale for these efforts is that society as a whole gains from them. It is important that state subsidies be used to ensure that interventions to manage for resistance do not reduce patients' access to effective and affordable drugs.

Huge gains in life expectancy have come from the introduction of effective drugs to treat infectious diseases. Our history of treating infections successfully is brief, however, and dates back only 50 or 60 years. Sustaining this ability in the long term

requires a willingness to invest in interventions both to extend the therapeutic life of existing drugs and to discover and develop new ones. Some of these interventions, such as better infection control, introduction of affordable vaccines, and proper dosing, would benefit patients immediately; others, such as using combination treatments for malaria and investing in new drugs, may not bear fruit in the near term. Without a sustainable, long-term vision of coexistence with harmful microbes and imaginative solutions to the problem of resistance, our ability to control infectious diseases stands in peril.

## NOTE

1. The fitness cost of resistance is an evolutionary disadvantage placed on resistant pathogens. However, some argue that although most resistance-determining mutations engender some fitness cost, these costs are likely to be ameliorated by subsequent compensatory mutations.

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