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Controlling Infectious Diseases

by Mary M. Kent and Sandra Yin

Including Special Sections on
Diarrheal Diseases, Malaria, Tuberculosis, and Pandemics

- Young children account for one-half of the deaths from infectious diseases.
- Better sanitation, antibiotics, and vaccines can control most of the serious infectious diseases.
- Infectious microbes continue to evolve, requiring new methods and drugs for their control.

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Special Sections

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Controlling Infectious Diseases

by Mary M. Kent and Sandra Yin

The 20th century was a triumph for human health and longevity. An Indian born in 1900 had a life expectancy of 22 years; an American baby born that year could expect to live about 49 years. By century's end life expectancy had soared to unprecedented levels even in many poor countries. In 2005, average life expectancy at birth in the United States was 78 years; in India it was 62 years.[1]

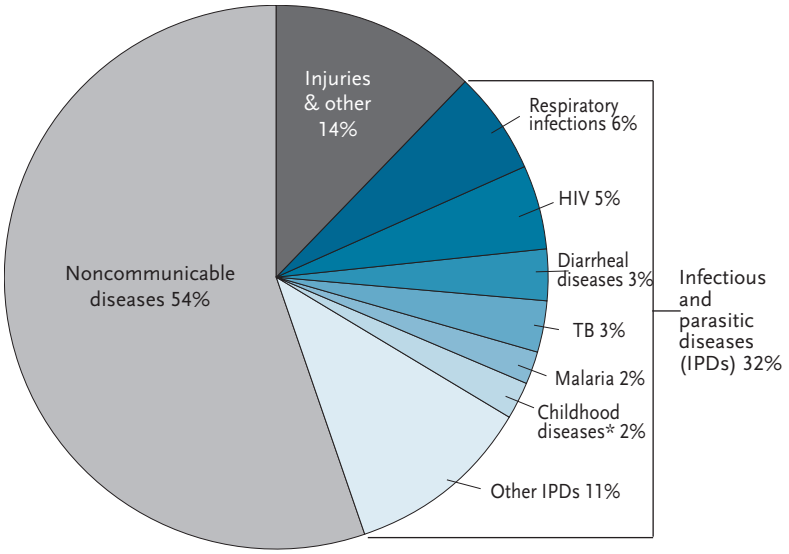
The falling death toll from infectious diseases—primarily among infants and young children—led to these spectacular improvements in human life expectancy. For most of human history, communicable diseases such as malaria, smallpox, and tuberculosis (TB) were leading causes of death. TB was the second-highest cause of death in the United States in 1900, and malaria was a major problem in southeastern U.S. states. These diseases were effectively controlled in the United States and declined throughout much of the world in the 20th century. One major disease—smallpox—was virtually wiped out; another—polio—may be close to eradication.[2]

Improvements in sanitation and the development of vaccines and antibiotics accelerated the decline of infectious and parasitic diseases (IPDs) in the 20th century.

But, with a few exceptions, communicable diseases have not been vanquished. The microbes that cause these diseases continue to evolve, sometimes requiring new drugs and methods to combat them. New pathogens emerge, or make the jump from infecting animals to infecting humans. The most recent global estimates show that communicable diseases cause about one-third of all deaths (see Figure 1). Pneumonia and other lower respiratory diseases are the largest group, followed by HIV/AIDS, diarrheal diseases, TB, and malaria.

Communicable diseases impose vastly different health burdens on the wealthy and poor. They are the primary reason why a baby born in Somalia today is 30 times more likely to die in infancy than a baby born in France.[3] Most of these diseases—including measles, HIV, TB, and malaria—are preventable and treatable using proven and often surprisingly low-cost health interventions. But control of communicable diseases will require additional financial investments, fundamental improvements in health delivery, and longer-term political commitments.[4]

Figure 1
Global Deaths by Leading Cause, 2002



Note: As used here, IPDs include infectious and parasitic diseases and communicable respiratory infections.

*Pertussis, poliomyelitis, diphtheria, measles, and tetanus.

Source: World Health Organization, *The World Health Report 2004* (2005): annex table 2.

International and national organizations such as the U.S. Agency for International Development (USAID), the World Health Organization (WHO), the World Bank, and UNICEF—aided by private funders such as the Bill & Melinda Gates Foundation—have spearheaded major efforts to attack infectious diseases.

Large-scale vaccination campaigns, for example, save millions of lives from measles and whooping cough each year. Other diseases—such as malaria—have proved more difficult to control. Although greatly diminished worldwide, malaria has resurged in many countries and continues to be a leading cause of childhood deaths in Africa and a drag on health in several other regions. Likewise, TB, which lost its hold on Europe and the United States by the mid-20th century, continues to devastate the health of millions in developing countries—especially where HIV/AIDS is prevalent. TB is

re-emerging in many Eastern European countries where HIV is rapidly increasing.

Some of the miracle drugs that suppressed major diseases have lost their magic as viruses and parasites develop resistance to them. The mosquitoes that transmit malaria, dengue fever, and other diseases have become immune to some common insecticides. The parasites carried by mosquitoes have developed a resistance to drugs formerly used to treat them. Medical researchers are in a race to develop new weapons against disease-carrying pests, viruses, and parasites before the current arsenal is obsolete.

In the late-20th century, the world was also hit with a new pandemic—HIV—that infects more than 40 million people today and causes at least 3 million deaths annually. HIV undermines the immune system—causing AIDS and making it harder for HIV-infected individuals to fight other diseases. It has increased death and disability from other IPDs, especially TB.

Other infectious diseases have emerged that have proved especially lethal—including Ebola and hantaviruses. While outbreaks tend to be highly localized, some bioterrorism professionals fear these viruses could be used as weapons.[5] Influenza experts warn that we are likely to experience a worldwide influenza pandemic with the potential of causing millions of deaths, as did the Spanish Flu pandemic in the early 20th century. No one can predict when this might occur, or how deadly the next flu pandemic will be. The public health community is currently focused on the H5N1 avian flu, which is spreading around the world. H5N1 has not been transmitted person-to-person so far, but it could evolve into a major human health threat.[6]

Aspects of life in the 21st century—frequent travel, population migration, international trade, even climate change—all favor the spread and persistence of infectious and parasitic disease (IPDs). Dengue fever probably arrived in Latin America in recent decades as larvae in tire shipments from Asia, and cholera may have been carried in the holding tanks of freighters.[7] Both are now major health concerns in parts of Latin America. If average temperatures continue to rise throughout the world, the range of disease-carrying mosquitoes will expand, exposing more people to malaria and dengue, among other diseases.[8]

This *Population Bulletin* explores the major health threats from infectious and parasitic diseases, with a special focus on malaria, diarrheal diseases, and TB. It examines recent trends and obstacles to prevention and treatment. It will also look at the potential threats from new pandemics and what the international health community and national governments are doing about them.

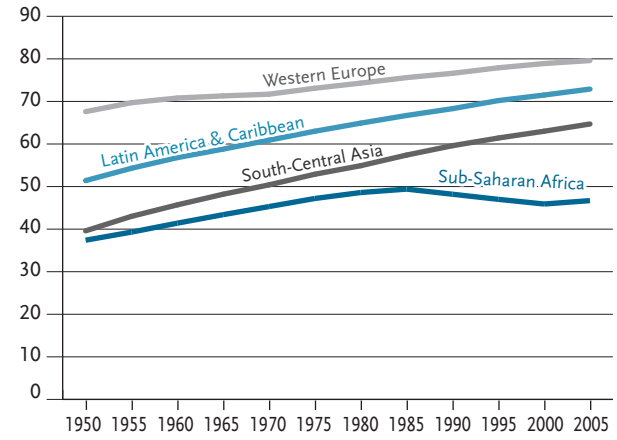
Demographic Dimension

For much of human history, populations grew slowly, if at all, because high birth rates were matched by high death rates from infectious diseases and other hazards. Major epidemics, such as the black plague that killed off one-third of Europe's population in the 13th century, and smallpox, which decimated the indigenous population of the Americas in 16th and 17th centuries, were extreme examples.[9] But tuberculosis, measles, pneumonia, and diarrheal diseases (including cholera and typhus) were constant threats. Living conditions improved in Europe after the 18th century because of a confluence of economic, political, and social developments, and a long stretch of moderate weather that made food more plentiful. But basic knowledge of what caused infectious disease was minimal. It wasn't until the late 19th century that medical researchers accepted the idea that invisible microorganisms transmitted disease through water, pests, food, or close personal contact.[10] On average, mortality remained quite high until the late 19th and early 20th centuries. After that time, several factors greatly reduced the mortality from IPDs, and ushered in an epidemiological transition to lower mortality:

- People learned the importance of better hygiene; especially washing hands and safely handling food, as knowledge of the "germ theory" of disease spread;
- Antibiotics and vaccines effective against IPDs became available; and
- Governments invested in clean water and sanitation systems.

Figure 2

Increase in Life Expectancy in Four World Regions, 1950–2005



Source: UN Population Division, *World Population Prospects: The 2004 Revision* (2005).

These developments occurred at different times in different countries—better hygiene and sanitation practices helped IPDs fall markedly in developed countries even before antibiotics and vaccines were widely available, for example.[11]

Death rates declined, but birth rates remained high in many countries, creating an unprecedented surplus of births over deaths and causing growth rates to surge. Birth rates began to decline as families realized that more of their babies would survive to adulthood, especially as families moved away from farming and other livelihoods in which having many children might be an advantage. As birth rates declined, population growth rates subsided in many countries throughout the world, especially in Europe and North America.

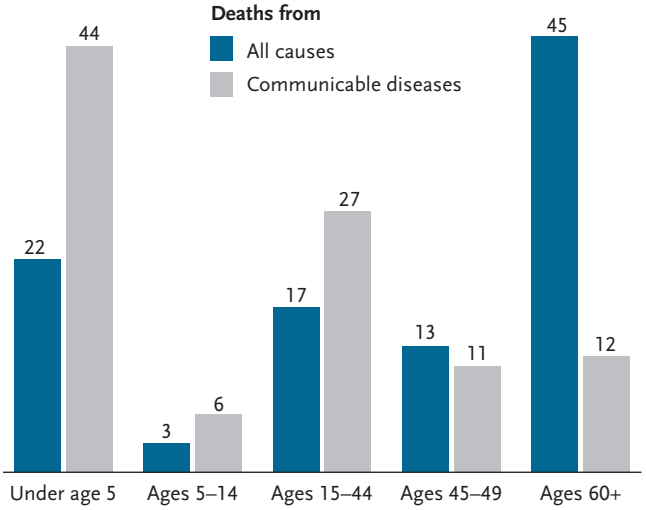
But infant and child mortality from infectious diseases is still too high in many developing countries and among disadvantaged groups in nearly every country. This is the primary reason for the life expectancy gap between low mortality Western Europe and higher-mortality sub-Saharan Africa and South-Central Asia (see Figure 2). Progress against IPDs in many low-income countries has lagged or stagnated because of a lack of resources, political instability, and corruption, among other barriers. HIV/AIDS epidemics have blocked progress in many sub-Saharan African countries.

The demographic toll of infectious diseases is reflected in the age and sex structure of high mortality countries. Except for AIDS and TB, the young are disproportionately affected by IPDs. Although children under age 15 account for one-quarter of all deaths in low- and middle-income countries, they account for one-half of the deaths from infectious and parasitic diseases, including lower respiratory infections (see Figure 3). More than 7 million children under age 15 die each year from IPDs, at least 85 percent die before their fifth birthday.

As IPDs are controlled, infant and child mortality rates could fall quickly, as they did in many countries in the 1950s and 1960s. This welcome improvement in child survival could produce other demographic effects: a bulge in the number of children in high-mortality countries and a spike in population size. The magnitude and length of any surge in population growth will depend on whether couples in those countries want to limit their childbearing and whether they have easy access to family planning services. We are not likely to see a repeat of the rapid global population growth of the 1960s and 1970s, in part because the remaining high mortality countries make up less than 10 percent of world population. Sustained and rapid growth is also unlikely because fertility in most countries is lower than it was in the 1960s and because family planning is more acceptable and available.

Figure 3

Percent of all Deaths and Deaths From Infectious Diseases by Age in Low- and Middle-Income Countries, 2001



Source: C.D. Mathers, A.D. Lopez, and C.J.L. Murray, "The Burden of Disease and Mortality by Condition," in *Global Burden of Disease and Risk Factors*, ed. A.D. Lopez et al. (2006): table 3B.1.

Geographic Disparities

The geographic disparities in the toll from infectious and parasitic diseases are most evident for children. In more developed regions, IPDs cause just 5 percent of deaths of children under age 5 (see Figure 4, page 6). This contrasts sharply with the percentages in lower- and middle-income countries. More than three-fourths of child deaths in Africa were attributed to infectious diseases around 2001, more than one-half in Southeast Asia, and just over one-third in Eastern Europe and in Latin America and the Caribbean.

Sub-Saharan Africa is the region plagued by the worst death and disability from IPDs, led by HIV/AIDS. Because of HIV, average life expectancy in southern Africa declined from 62 to 48 between the early 1990s and the early 2000s, reversing hard-won gains in life expectancy in the previous three decades.[12] HIV/AIDS is the largest single cause of illnesses and deaths in the region, accounting for 19 percent of deaths in 2001. Five other IPDs accounted for another 34 percent of deaths: malaria, lower respiratory diseases, diarrheal diseases, measles, and TB.[13]

Sub-Saharan Africa also suffers the most death and disability from communicable tropical diseases such as onchocerciasis (river blindness), trypanosomiasis (sleeping sickness), and helminth infections.[14]

South Asia—including Bangladesh and India—is the other major world region where poverty is widespread

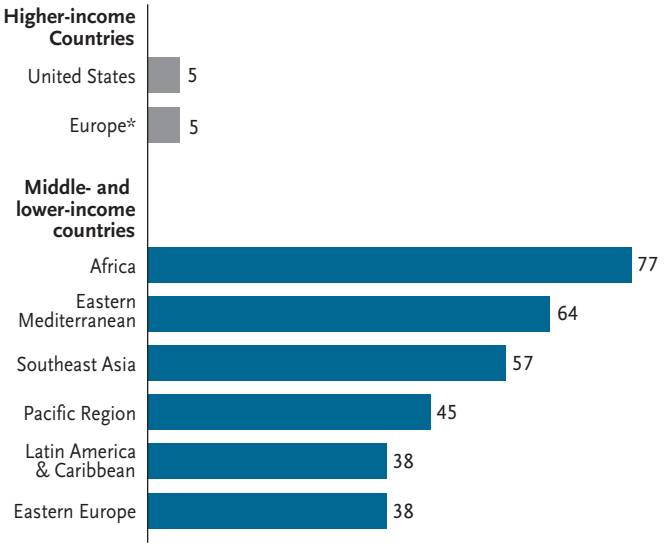
and where infectious diseases are a major health problem (see Table 1). The tropical and semitropical climates, poverty, and lack of adequate infrastructure and health care have hindered the fight against preventable infectious diseases in this region.

The leading IPDs in South Asia are lower respiratory diseases and diarrheal diseases, which especially target children. Other IPDs in the top 10 causes of death are TB and HIV/AIDS, which especially affect working-age adults. The HIV/AIDS epidemic has been another setback for disease control. Although HIV prevalence has remained far below the levels in southern Africa, it is a growing problem.

Countries in Latin America and the Caribbean have made more progress in controlling infectious diseases. IPDs caused less than 15 percent of all deaths, and 38 percent of deaths of children under age 5 in the region around 2001. The incidence of measles deaths, for example, has fallen markedly throughout the region, and, except for Haiti, HIV has not exceed 1 percent in most countries in the region.[15]

Some parasitic diseases, such as schistosomiasis, are endemic in parts of Latin America, and dengue fever and its more serious complication, dengue hemorrhagic fever, actually increased in urban areas during the 1990s.

Figure 4
Percent of Child Deaths From Infectious Diseases in Selected Regions, 2000–2003



* Excludes Eastern European countries.

Note: Regions follow WHO definitions, which differ from UN regions shown in Figure 2.

Source: World Health Organization, *The World Health Report 2005, Statistical Annex* (www.who.int, accessed April 1, 2006): tables 3 and 4.

Differences by Age

Pneumonia, diarrheal diseases, and malaria are the major causes of death for children under age 15—with the vast majority succumbing before age 5. Children who survive until their fifth birthdays have already fought off a number of childhood infections and have a good chance of living until age 15. The 5-to-14 age group in high-mortality countries tend to be a healthier group—they developed resistance to many IPDs and they are not yet subject to most of the health problems that harm adults, including complications of pregnancy and childbirth, TB, HIV, and such noncommunicable diseases such as cancer and cardiovascular diseases.

Table 1
Top 10 Causes of Death in Low- and Middle Imcome Countries, Selected Regions, 2001

	Latin America and the Caribbean	Sub-Saharan Africa	South Asia	Europe and Central Asia
1	Ischemic heart disease	**HIV/AIDS**	Ischemic heart disease	Ischemic heart disease
2	Cerebrovascular disease	**Malaria**	**Lower respiratory infections**	Cerebrovascular disease
3	Perinatal conditions	**Lower respiratory infections**	Perinatal conditions	Lung cancer*
4	Diabetes mellitus	**Diarrheal diseases**	Cerebrovascular disease	COPD
5	**Lower respiratory infections**	Perinatal conditions	**Diarrheal diseases**	Self-inflicted injuries
6	Violence	**Measles**	**Tuberculosis**	Hypertensive heart disease
7	COPD	Cerebrovascular disease	COPD	Poisonings
8	Road traffic accidents	Ischemic heart disease	**HIV/AIDS**	**Lower respiratory infections**
9	Hypertensive heart disease	**Tuberculosis**	Road traffic accidents	Cirrhosis of the liver
10	**HIV/AIDS**	Road traffic accidents	Self-inflicted injuries	Stomach cancer

Note: Communicable disease (infectious and parasitic, including lower respiratory infections) are in **bold**.
COPD: Chronic obstructive pulmonary disease
* includes trachea and bronchus cancers

Source: C.D. Mathers, A.D. Lopez, and C.J.L. Murray, "The Burden of Disease and Mortality by Condition," in *Global Burden of Disease and Risk Factors*, ed. A.D. Lopez et al. (2006): table 3.10.

HIV/AIDS, TB, and lower respiratory infections (especially pneumonia) are the top three infectious diseases that strike those ages 15 to 59. People age 60 or older are most likely to die of a noncommunicable disease, including heart disease, cancer, and stroke, but older people also succumb to infectious diseases. Pneumonia is a major cause of death to the elderly in all countries. Older people often have several health problems that make them less able to recover from respiratory infections. People whose immune systems are compromised by TB and malaria and other parasitic infections are especially vulnerable. In low- and middle-income countries, lower respiratory diseases, TB, and HIV are the top three causes for people age 60 or older.

Childhood Diseases

A relatively small number of infectious diseases are responsible for 62 percent of deaths to children under age 5 in low- and middle-income countries.[16] Children rarely die from these causes in more developed countries because of widespread vaccination, greater access to health care, and better hygiene and sanitation. Less developed countries have made great strides in combating IPDs, and infant mortality rates have declined in most regions. But the gap between rich and poor countries remains substantial.

In 1974, WHO launched the Expanded Programme of Immunization (EPI), with the aim of vaccinating all children against six major childhood killers: whooping cough (pertussis), diphtheria, tetanus, polio, measles, and childhood tuberculosis. Three doses of the vaccines for pertussis, diphtheria, and tetanus are required during the child's first year of life for full protection—meaning three separate visits with health-care workers. The polio vaccine also requires additional doses. By 2004, at least three-fourths of children in less developed countries were protected by at least one of the EPI vaccines, and coverage was above 90 percent in some regions. Yet maintaining these high coverage rates for each new generation of children is an ongoing challenge in resource-constrained countries.

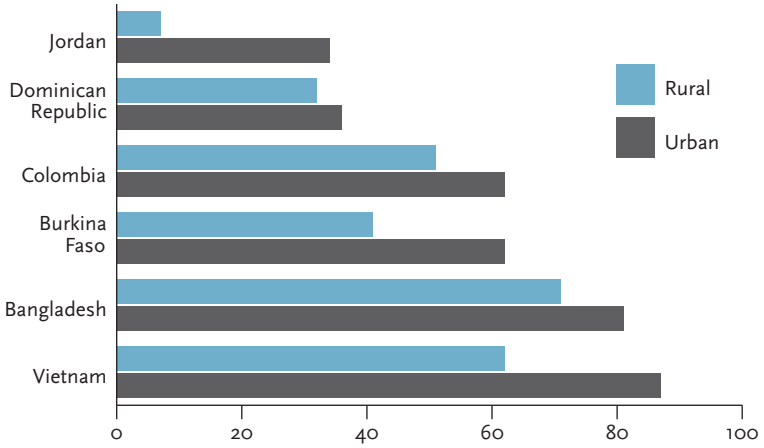
Vaccination rates are still quite low in many countries. Fewer than one-half of the children in the Dominican Republic, Haiti, and Jordan were protected from all six EPI target diseases, as were fewer than one-fifth of children in Chad, Ethiopia, and Nigeria.[17] Within countries, children living in rural areas are often much less likely to have received all their vaccinations. In Jordan, just 7 percent of children in rural areas were vaccinated in 2002, compared with 34 percent of urban children. In Vietnam, the rural rate was 62, compared with 87 in urban areas (see Figure 5). In Bangladesh, in contrast, the gap between urban and rural is smaller and the overall percentage fully vaccinated is much higher, demonstrating that low-income and largely rural countries can achieve high vaccination rates.

Infant and child mortality is greater in rural areas of most countries. In Bolivia, 81 infants died per 1,000 births in rural areas around 2003, for example, compared with 57 deaths per 1,000 births in urban areas.[18]

But the WHO immunization programs have saved millions of lives and have nearly eliminated polio. Around 2001, measles was still claiming at least 676,000 lives per year, but vaccine coverage had averted more than 1 million deaths (see Table 2, page 8). The pertussis vaccine averted more than another 1 million deaths, according to estimates.

EPI has been expanded and additional vaccines are being developed and administered. In particular, many less developed countries are vaccinating children against hepatitis B, yellow fever, and a deadly strain of influenza (Haemophilus influenzae type b, or Hib). A vaccine to protect children against the rotavirus—which causes severe diarrhea—may soon be available in less developed countries, with the potential of saving thousands of lives each year. Vaccines against meningitis and pneumococcal disease may also become available, further cutting the disease burden from IPDs.[19]

Figure 5
Percent of Children Fully Vaccinated, by Residence, Selected Countries, 2002-2005



Note: Percentage refers to children ages 12 to 23 months who have received the BCG vaccine for childhood tuberculosis, the measles and polio vaccines, and three doses of the vaccines for diphtheria, pertussis, and tetanus (DPT).

Source: ORC Macro, StatCompiler, www.measuredhs.org, accessed May 5, 2006.

Table 2
Vaccine-Preventable Childhood Diseases, 2001

Disease	Number of deaths (thousands)	Deaths averted by vaccine (thousands)
Measles	676	1,237
Hepatitis B	600	<1
Hib (influenza)	463	5
Pertussis	301	1,042
Tetanus	293	643
Yellow Fever	30	33
Diphtheria	5	73
Polio	<1	51

Note: Diseases in **bold** were part of the original WHO Expanded Programme of Immunization Project (EPI), which has had broader coverage for a longer period of time than other vaccines.

Source: L. Brenzel et al., "Vaccine-Preventable Diseases," in *Disease Control Priorities in Developing Countries*, 2d ed., ed. D.T. Jamison et al. (2006): table 20.2.

Disability and Ill Health

While the IPDs cause excess and often preventable deaths, their total effect on global health is much greater. Infectious diseases affect physical and mental growth in childhood, which can cause life-long disabilities that impair a person's ability to support themselves and their families. Pneumonia, which is responsible for about one-fifth of deaths of children under age 5, can permanently damage lungs. Measles can lead to blindness, polio to crippling, and hepatitis to liver cancer, for example. Malaria in pregnant women can cause low birth-weight babies, which can lead to a host of developmental problems. Malaria and other parasitic diseases often produce severe anemia, which can render their victims unable to work. Skin diseases can disfigure or disable victims, affecting their ability to function normally in society.[20]

Many people suffer from more than one IPD, which may be exacerbated by other health problems—especially malnutrition. WHO estimates that malnutrition is the underlying cause of more than one-half of the deaths among children under age 5.

Helminth infections caused by parasitic worms are examples of IPDs that rarely cause death directly but undermine health in ways that can affect all aspects of an individual's life. Some helminth infections are transmitted by close contact with soil or water containing the parasites, which links them to poor living conditions. They tend to thrive in warm climates in tropical and subtropical areas. The persistence of some helminths, such as schistosomiasis, has been attributed to building of dams and other construction projects that alter the flow of waterways in ways that promote the growth of the snail that is integral to the parasite's life cycle. As such, an increase in schistosomiasis can be an unintended consequence of economic development.

Helminth infections can thwart educational advancement and hinder economic development. The severe anemia triggered by helminth infections in children can stunt physical growth, undermine physical fitness, and cause behavior-related problems. These infections can also cause chronic urinary and kidney problems in adults. Disability, pain, and undernutrition hinder individuals' ability to contribute to society and the economy. Such infestations can be prevented by using clean water, handwashing, and disposing of human wastes adequately. Routine deworming programs in schools have proved highly effective against some of the most common parasitic infections.[21]

The total health burden of a disease can be estimated by combining the estimated years of life lost prematurely by people who died of the disease, and the number of years of disability caused by the disease. Malaria, for example, caused an estimated 2 million deaths in 2002, but was responsible for the loss of 46 million disability-adjusted life years, or DALYs (see Table 3). The DALYs lost because of schistosomiasis in 2002 were more than 100 times the number of deaths from the disease. Each DALY represents one lost year of health.

Table 3
Deaths and DALYs Caused by Selected Communicable Diseases, 2002

	Deaths (millions)	DALYs (millions)
Communicable diseases	57.0	610.3
Tuberculosis	**2.7**	**34.7**
HIV/AIDS	**3.1**	**84.5**
Diarrheal diseases	**3.2**	**62.0**
Measles	**1.1**	**21.5**
Malaria	**2.2**	**46.5**
Schistosomiasis	**0.02**	**1.7**
Lower respiratory infections	**3.9**	**91.4**

Note: The disability adjusted life year (DALY) is a summary measure that includes the number of years of life lost to a premature death plus the number of unheatlhy years lived because of a specific cause of death.

Source: WHO, *Global Burden of Disease Estimates for 2002*, accessed online at www.who.int, on May 5, 2006.

Conclusion

Reducing the health burden from communicable diseases is a top priority for the international community. Two of eight millennium development goals (MDGs) embraced by all members of the United Nations in 2000 deal specifically with infectious diseases:

- Reduce the child mortality rate to two-thirds the 1990 level by 2015. Because IPDs causes at least one-half of deaths to children under age 5, this cannot be achieved without drastic reduction in communicable diseases.
- Combat HIV, malaria, and TB, among other diseases. This MDG not only calls for halting the spread of these diseases, but for reducing their incidence in the population by 2015.

Because health affects and is affected by so many aspects of life, the fight against communicable diseases is advanced by efforts to meet all the MDGs, including eradicating poverty and hunger, achieving universal primary education, promoting gender equality, improving maternal health, and ensuring environmental sustainability.

The means for preventing or controlling the major infectious diseases already exist—and are affordable even in poor countries. The most cost-effective health interventions have been documented by the monumental Disease Control Priorities Project and released in 2006.[22] If these measures are implemented around the world—for example fully vaccinating children, providing insecticide-treated bednets to combat malaria, and improving basic health services for children—the health burden from infectious diseases could be drastically reduced. And, new vaccines and drugs offer hope in the fight against the most pernicious communicable diseases.

The control of IPDs is an ongoing endeavor. We can eliminate unnecessary death and disability, but we will always face the threat of new and evolving microbes. As American historian William McNeill has stated:

"Ingenuity, knowledge, and organization alter but cannot cancel humanity's vulnerability to invasion by parasitic forms of life. Infectious disease which antedated the emergence of humankind will last as long as humanity itself…"[23]

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Special Section: Diarrheal Diseases

by Olivier Fontaine and Cynthia Boschi-Pinto

Two decades ago diarrhea was responsible for around 5 million deaths of children under age 5 each year. Now diarrheal diseases account for less than 2 million child deaths a year, thanks to major public health efforts to prevent and treat dehydration, the main cause of death from diarrheal disease.

Diarrhea causes severe loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate). Children can become dehydrated when these losses are not replaced adequately. The early stages of dehydration present no signs or symptoms. As dehydration increases, children may exhibit thirst, restless or irritable behavior, sunken eyes, and less elastic or supple skin.[1] In infants, the soft boneless areas in the skull may be sunken.

These symptoms become more pronounced in a child (or adult) suffering severe dehydration, and the child may go into shock, which may be characterized by diminished consciousness, lack of urine output, cool moist extremities, a rapid and feeble pulse, and low or undetectable blood pressure. If the child is not rehydrated promptly, death quickly ensues. Dehydration from diarrhea can be prevented by providing the child more fluids than usual, and/or increased frequency of breastfeeding, during acute episodes.

Decreased food intake, decreased nutrient absorption, and increased nutrient requirements during diarrhea episodes often combine to cause weight loss and failure to grow: The child's nutritional status declines and any preexisting malnutrition is made worse. In turn, malnutrition contributes to even more severe and frequent diarrhea. One can prevent the nutritional consequences of diarrhea by ensuring that children continue to feed during diarrhea and increasing food intake afterward.[2]

Increasing the intake of fluids a child would normally drink, supplemented by oral rehydration salts (ORS) to treat dehydration together with continued feeding to prevent malnutrition have proven to be powerful interventions for the prevention of childhood deaths from diarrhea.

In many countries, the decline in diarrhea mortality observed over the years is linked to the increased use of oral rehydration therapy (ORT), defined as "increased administration of fluids plus continued feeding," the public health intervention recommended by WHO and UNICEF.[3] However, diarrheal diseases remain a leading cause of preventable death, especially among children under age 5 in developing countries.

The Scope of the Problem

Of the 10.6 million child deaths a year globally, 1.9 million, or 18 percent, are related to diarrheal diseases. Almost all (98 percent) of the 1.9 million diarrheal deaths occur in low- and middle-income countries. Forty percent of all diarrheal deaths are in Africa and 32 percent in South and Southeast Asia. Moreover, country-specific estimates have revealed that just 15 countries (eight in sub-Saharan Africa and four in South and Southeast Asia) account for about 70 percent (1.3 million) of all diarrheal deaths worldwide. In the developing world, mortality rates are about twice as high in infants than in children ages 1 to 4.[4]

While the estimated number of deaths due to diarrhea have declined markedly over the last two decades, the incidence of diarrhea has declined very little. Between the 1980s and 2000, there were between two and three episodes of diarrhea per child under 5 per year. Since 1990, some studies show a slight increase in diarrhea incidence rates.[5] Morbidity rates have been consistently greatest among infants ages 6 to 11 months.[6]

Of the 1.9 million deaths due to diarrhea, 61 percent are associated with undernutrition.[7] Diarrhea and malnutrition reinforce one another in a potentially deadly spiral: Frequent and prolonged episodes of diarrhea can lead to malnutrition, and malnutrition can facilitate the evolution of diarrhea towards death. Children living in poor households are more likely to be exposed to health risks, less resistant to disease, and less likely to receive appropriate care from a health provider.[8] In addition, the main risk factors for developing diarrheal disease—poor access to water and sanitation, improper hygiene and feces disposal practices at home, poor housing, and crowding—are intrinsically linked to poverty. In the African region, where the proportion of diarrhea deaths is highest, approximately one-half of the population has no access to safe water

and two-thirds lack access to hygienic sanitation.[9] Disparities within countries also illustrate income inequalities: Diarrhea prevalence in some countries is almost twice as high among the poorest 20 percent of the population as it is among the richest 20 percent (see figure).

The long-term consequences of diarrheal diseases remain poorly understood. However, repeated diarrheal episodes can affect a person's overall intellectual capacity and concentration.[10] In addition, early childhood malnutrition—a common consequence of repeated episodes of diarrhea—reduces physical fitness and work productivity in adults.[11]

Successful Preventive Interventions

Strategies to control and treat diarrheal diseases have remained relatively unchanged since the 1980s. Seven effective interventions continue to be high priorities:

- Breastfeeding;
- Improvement in weaning practices;
- Rotavirus immunization;
- Cholera immunization;
- Measles immunization;
- Improvement of water supply and sanitation facilities; and
- Promotion of personal and domestic hygiene.

Promoting Exclusive Breastfeeding

Breastfed children under age 6 months are six times less likely to die of diarrhea than infants who are not breastfed.[12] In 1984, researchers estimated that exclusive breastfeeding could reduce diarrheal deaths by 24 percent to 27 percent in the first six months of life.[13] Based on this evidence, exclusive breastfeeding for the first six months of life has been promoted as an important weapon against diarrhea. Breastfeeding is encouraged—and early bottlefeeding discouraged—through hospital policies and actions; counseling and education by peers or health workers, mass media campaigns, community education, and mothers' support groups; and implementation of the International Code of Marketing of Breastmilk Substitutes. This code is designed to ensure adequate information about the importance of breastfeeding young infants and appropriate marketing and distribution of breast milk substitutes. Increases in exclusive breastfeeding as a result of education and promotion have been associated with a significant reduction in the risk of diarrhea.[14]

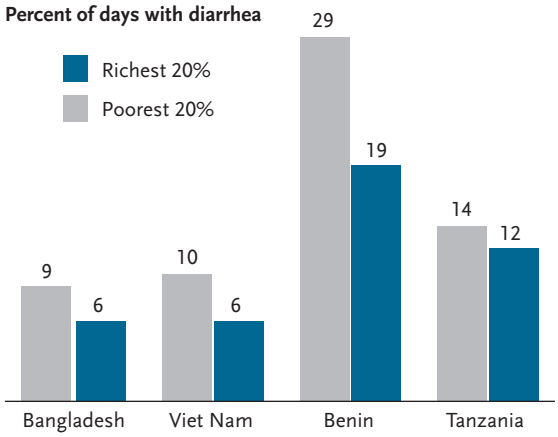
Complementary Feeding

Complementary feeding, in which an infant transitions from exclusive breastfeeding to normal family foods, typically occurs between 6 months and 18 to 24 months of age. It is a very vulnerable period for infants' health. All infants should start receiving foods in addition to breast milk after 6 months of age. The complementary foods should be at least as nutritious as breast milk, they should provide enough calories for a developing child, and they should be appealing enough for the child to eat. To minimize the risk of contamination with pathogens, all food should be prepared and served under hygienic conditions.

Improved complementary feeding practices to prevent or treat malnutrition could save as many as 800,000 lives per year.[15] While the increased incidence of diarrhea associated with the introduction of foods in addition to breast milk feeding has been recognized for a long time, two key risk factors have not received sufficient attention: feeding with contaminated foods, and failing to provide appropriate nutrients during and after a diarrheal episode.[16] Several interventions have been proposed to reduce microbial contamination of common foods, including education, improved household storage of foods, reduced pathogen multiplication in food (such as food fermentation), and the use of probiotics, nonpathogenic organisms (Lactobacillus GG) that colonize the gut and create an environment that resists infection by pathogens.[17] However, the effectiveness of these techniques has not been adequately evaluated.

While mothers and other caregivers are told to introduce infants to the foods eaten by the whole family, it is

Diarrhea Prevalence in Under-5 Children by Socioeconomic Status in Selected Countries, 2002



Source: C. Victora et al., *Lancet* (July 19, 2003): 233-41.

practically impossible to meet all of an infant's essential micronutrient requirements with unfortified foods, especially in places where meat, fish, and dairy products are limited.[18] While vitamin A supplementation may not significantly reduce the incidence of diarrhea and other common childhood illness, it may reduce the incidence of severe diarrhea and mortality due to gastroenteritis.[19] Adding zinc to the diet can also reduce the incidence of diarrhea.[20]

Advances in Management

Two recent advances in managing diarrheal disease—newly formulated oral rehydration salts (ORS) containing lower concentrations of glucose and salts, and zinc supplementation—can drastically reduce the number of child deaths. These new advances, used in addition to prevention and treatment of dehydration with appropriate fluids, breastfeeding, continued feeding and selective use of antibiotics, will reduce the incidence, duration, and severity of diarrheal episodes.

New Oral Rehydration Salts (ORS) solution

To improve acceptance of ORS solution by mothers and health workers, researchers developed an ORS solution that could not only prevent or treat dehydration from all types of diarrhea, but provide other important clinical benefits. Reducing the solution's salt and glucose content reduced stool output, vomiting, and especially, the need for intravenous fluids. Rehydration salts with lower salt and glucose content could substantially reduce childhood deaths from diarrhea (except for cholera), especially in areas where intravenous fluids or the skills to administer them are not available.[21] Based on this finding, WHO and UNICEF launched the new ORS solution in May 2002 and included it in the WHO model list of essential medicines in March 2003. Since January 2004, the new ORS formulation is the only one procured by UNICEF.

Zinc Supplementation

When a zinc supplement is given during an episode of acute diarrhea, it reduces the episode's duration and severity.[22] In addition, zinc supplements given for 10 to 14 days lower the incidence of diarrhea in the following two to three months.[23] Using zinc to manage diarrhea could save 300,000 children each year.[24] Accordingly, WHO and UNICEF have issued new recommendations for the clinical management of diarrhea. Along with increased fluids (ORS solution or home-made fluids) and continued feeding, all children with acute diarrhea should be given zinc supplements for 10 to 14 days.[25]

There is now good evidence that the promotion of oral rehydration therapy with other key preventive and curative interventions have played a large role in the welcome reduction in childhood deaths caused by diarrhea.[26] To reach the United Nations Millennium Development Goal (MDG) of reducing the 1990 mortality rate among children under 5 by two-thirds by 2015, the challenge for the next decade will be to increase or ensure universal coverage of these interventions in developing countries.

To meet this challenge, health worker capacity must be maintained to ensure that all mothers and caretakers are taught:

- To prevent dehydration through early administration of increased amounts of appropriate fluids available in the home (and ORS solution, if on hand);
- To continue feeding (or increase breastfeeding) during the episode and increase all feeding after the episode;
- To recognize the signs of dehydration and the need for medical care; and
- To provide children with 20 milligrams per day of zinc for 10 to 14 days.

Over the long term, the most promising improvements in child health will come from integrating health care through initiatives such as the Integrated Management of Childhood Illness (IMCI), which promotes the accurate identification of childhood illnesses, ensures appropriate combined treatment of all major illnesses, strengthens the counseling of caretakers, and speeds up the referral of severely ill children. However, in low-resource settings, immediate action may be still be necessary to quickly reduce the high disease burden of diarrhea.

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Special Section: Malaria

by Sandra Yin

In 1955, malariologist Paul Russell wrote in the preface to *Man's Mastery of Malaria* that one could be confident that "malaria is well on its way towards oblivion."[1]

His prediction was too optimistic. While large-scale insecticide spraying and the widespread use of the miracle drug chloroquine freed millions of people from the grip of malaria in the decades after World War II, this relief was halted in many areas. The emergence of drug resistance, widespread resistance to available insecticides, and deterioration of national control programs suggest we are losing the battle. Malaria is reappearing in areas of the world formerly deemed disease-free.[2]

Each year, malaria kills up to 3 million people. It threatens close to one-half the world's population, and more than 1 million children die each year of complications related to malaria. Almost 5 billion clinical episodes resembling malaria occur each year, with more than 90 percent of the burden occurring in Africa.[3]

Malaria can be debilitating for people who live with the disease. It is characterized by extreme exhaustion and associated with high fever, sweating, shaking chills, and anemia.[4] Through chronic malaria-induced anemia and time lost or wasted in the classroom due to illness, malaria can have long-term effects on a child's cognitive development.

Malaria also causes and perpetuates poverty. Couples may have more children than they otherwise would because they fear losing a child to the disease. People living with the disease are less productive and earn less household income. Regions with endemic malaria have substantially lower economic growth rates than neighboring regions where malaria has been controlled. Fear of malaria has blocked foreign investment, tourism, and trade.

Who Is Most at Risk?

Malaria is an infection caused by a parasite of the genus Plasmodium. Of the four species of Plasmodium that infect humans, *P. falciparum* causes most of the severe disease and deaths attributable to malaria. It is most prevalent in sub-Saharan Africa and in certain parts of South Asia, Southeast Asia, and the Western Pacific.

The mosquito vector plays a crucial role in the malaria parasite's life cycle. The disease is transmitted when female Anopheles mosquitoes that carry the malaria parasite bite humans.[5]

Climate and ecology determine the distribution of the mosquitoes that carry the malaria parasites, and in turn the prevalence and severity of the disease. Malaria is endemic only in tropical and subtropical zones—in parts of Asia, Africa, Central and South America, Oceania, and some Caribbean islands (see figure).

Adults living in regions where malaria is endemic develop immunity, but pregnancy reduces a woman's immunity, raising her risk of death or severe anemia. Malaria infection in a pregnant woman may also result in spontaneous abortion, neonatal death, and low birthweight babies.

Malaria accounts for 1 in 5 childhood deaths in Africa. About three-fourths of all deaths due to malaria infections occur in African children younger than 5 who are infected with *P. falciparum*.

Patterns of malaria transmission and disease vary markedly among regions and within individual countries due to variations among malaria parasites and mosquito vectors, ecological conditions that affect malaria transmission, and quality of housing. Malaria disproportionately affects the poorest of the poor within those countries: 58 percent of the cases occur in the poorest 20 percent of the world population.[6]

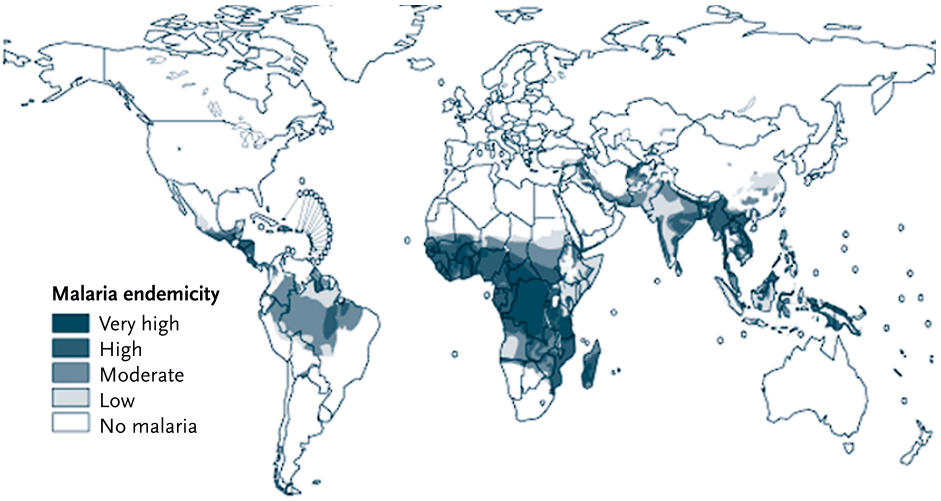
The increase in human population worldwide over the past century has influenced the percentage of the human population exposed to malaria risk. Despite human activities that reduced by half the land area supporting malaria, demographic changes resulted in a 2 billion increase in the total population exposed to risk of malaria because of continued population growth in malaria-endemic areas.[7] The population at risk in Africa grew from 60 million to 650 million. Southeast and South Asia, which is dominated by India, saw even more dramatic growth, from 200 million to 1.5 billion people at risk.

Malaria's Comeback

In the 1950s and 1960s, DDT spraying, elimination of mosquito breeding sites, and the use of antimalarial drugs freed more than 500 million people from the threat of malaria.[8] But the use of DDT to control malaria became highly controversial, and many countries banned or reduced its use beginning in the 1970s.

Evidence of DDT's harmful effects on wildlife, including thinning eggshells in birds and reproductive or endocrine deformities in reptiles, raised fears that long-term use would harm human health and destroy some animal species. Much of the developed world banned most uses of DDT by 1972. Many international donors were reluctant to fund DDT-spraying programs in developing countries.[9] The abandonment of DDT was followed by a resurgence of malaria in some areas.

Countries at Risk of Malaria Transimssion, 2001



Source: WHO, *Malarial Endemicity*, www.who.int, accessed May 21, 2006.

During the 1980s and 1990s, malaria increased in Africa for several reasons, including increased resistance to chloroquine, the most commonly used antimalarial drug; the deterioration of primary health services in many areas; and the emerging resistance of mosquitoes to insecticides. New breeding grounds for mosquitoes were created by dams and irrigation projects. During the past decade, malaria also resurged or intensified in South and Southeast Asia after eradication efforts were interrupted. It has reemerged in several Central Asian republics and in other former Soviet republics due in part to weakened public health infrastructure.[10]

Prevention

Long before the 19th century, when researchers discovered that mosquitoes spread malaria, people developed ways to avoid mosquito bites. In the 5th century B.C.E., Egyptians who lived in marshy lowlands slept under fishing nets steeped in fish oil to repel mosquitoes.[11]

Centuries later, during World War II, American forces in the South Pacific dipped bed nets and hammocks in DDT. After DDT use was discouraged or banned, bed nets were treated with biodegradable insecticides called pyrethroids.

Pyrethroid-treated nets paired with antimalarial drugs halved mortality in children younger than 5 in the Gambia. The nets are credited with saving many lives in Kenya, Ghana, and Burkina Faso.

ITNs have some drawbacks. At $2 to $6 each, nets are too expensive for many of the people who need them most. Nets usually have to be redipped every six to 12 months to remain effective. Some newly developed nets, however, promise longer-lasting protection. The nets are impregnated with an insecticide that lasts four to five years.

Indoor residual spraying can be a highly effective method for malaria vector control. It reduces human and mosquito contact by repelling some mosquitoes before they enter a dwelling and killing others that alight on treated walls after a blood meal. Such spraying can achieve a rapid reduction in transmission during epidemics and other emergency situations, provided it is well-timed and has wide coverage.

Public health officials in malarious countries see the reintroduction of DDT as integral to malaria control—particularly as they confront a growing resistance to other, more costly pesticides and hardier, more drug-resistant parasites. Health officials say the current use indoor spraying of DDT for disease vector control releases only tiny amounts of DDT, compared with more destructive wide-area crop spraying of the 1950s.[12]

WHO currently recommends indoor residual spraying of DDT for malaria vector control. In some parts of the world, this long-lasting toxin offers the best hope for reining in malaria.

The dwindling availability of low-risk and cost-effective insecticides poses an ongoing challenge to malaria control. In areas of intense malaria transmission, use of insecticide-treated nets is more sustainable.

In areas of high and stable transmission of falciparum malaria, intermittent preventive treatment (IPT) is recommended for pregnant women. It usually consists of two curative doses of antimalarial treatment given during prenatal care visits. IPT can significantly reduced the incidence of severe maternal anemia and low birthweight births.[13]

Treatment

The most effective drug treatments vary depending on a host of factors including the type of malaria parasite involved and how stable the transmission of malaria is. All

malarious countries and territories have national malarial treatment policies. Ideally, health workers monitor the effectiveness of drugs closely and change treatments when parasite resistance to chloroquine and other drugs emerges. In many malaria-endemic areas, ongoing obstacles to speedy diagnosis and effective drug treatment persist. Among them: unreliable microscopy, widespread distribution and use of substandard and counterfeit drugs.

Drug Resistance

Antimalarial drug resistance presents one of the biggest challenges in malaria control.

While the former "miracle drug," chloroquine, is losing effectiveness against ever more robust forms of the malaria parasite, it remains a top-selling antimalarial drug in Africa. The next most affordable drug in Africa, sulfadoxine-pyrimethamine, is also coming up against ever more hardy and resistant strains of *P. falciparum*.

In response to widespread resistance of *P. falciparum* to monotherapy, or single drug therapies, with conventional antimalarial drugs such as chloroquine, WHO now recommends combination therapies as the treatment policy for falciparum malaria. Malaria experts believe combinations of drugs will work, especially if they include a form of *artemisia annua*, a medicinal herb once used as a fever remedy in ancient China. Artemisinins fight malaria parasites more quickly than any other treatment and also block malaria's spread from humans to mosquitoes. If used alone, the artemisinins will cure falciparum malaria in seven days. In combination with certain synthetic drugs, artemisinin-based combination therapies (ACT) produce high cure rates in three days. They can also retard the development of resistance to the partner drug. But artemisinins cost 10 to 20 times more than weaker malaria drugs, including chloroquine. And the global supply of ACTs is tight.

Since 2001, WHO has recommended that artemisinin be used only in combination with other antimalarials to prevent the malaria parasite from developing artemisinin resistance. In January 2006, the head of WHO's malaria section warned that using artemisinin alone could leave the world with no effective weapon against malaria. "We can't afford to lose artemisinin," said Arata Kochi, head of WHO's Roll Back Malaria department. "If we do, it will be at least 10 years before a drug that good is discovered."[14]

Kochi, a physician who earlier headed WHO's TB program against tuberculosis, said he was trying to prevent a repeat of what happened to TB—the emergence of strains that are resistant to all drugs. By mid-May 2006, 13 drug companies agreed to comply with WHO's recommendation to phase out single-drug artemisinin medicines and focus on producing ACTs.[15]

In an ideal world, countries where malaria is endemic could institute policies that include insecticide-treated nets, indoor residual spraying, and IPT. But the cost of mounting such a campaign could be too high. In resource-poor areas, insecticide-treated nets would be the most cost-effective preventive measure.

While malaria has attracted both funding and the attention of international organizations, it remains a major global problem that exacts a heavy toll on the health and economic life of the world's poorest communities. Before the battle against malaria is over, more research is needed to improve existing interventions and develop new weapons to fight malaria.

In 1958, WHO, the Pan American Sanitary Bureau, and other international organizations aided governments in a fight against malaria. The goal was to wipe malaria off the face of the earth in 10 years. Today's goals are more limited. There's no talk of eradicating malaria. The Millennium Development Goal accepted by 190 countries in 2000 calls for a halt the spread of malaria and progress in reversing its incidence by 2015.

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Special Section: Tuberculosis

by Sandra Yin

Humans have had a long relationship with TB: Evidence of TB has been found in ancient mummies in Egypt and Peru. As late as 1900, TB was the second most common cause of death in the United States. Although TB is no longer a major killer in most developed countries, it remains the world's deadliest curable infectious disease. One-third of the world population is currently infected with the bacillus that causes TB. People infected with latent TB have a 10 percent to 20 percent risk of developing active TB, which, untreated, can lead to debilitating illness and death. Although drugs to cure TB have been around since the 1940s, approximately 2 million people died from TB in 2004; another 3.9 million new cases of the most infectious form of TB appeared that year.[1]

Developing countries bear the brunt of the TB epidemic. An estimated 95 percent of TB cases and 98 percent of TB deaths occur in the developing world. Just five countries—Bangladesh, China, India, Indonesia, and Pakistan—account for nearly half the new cases each year.[2]

The incidence of TB worldwide is growing by roughly 1 percent a year, driven primarily by the HIV epidemic. Accordingly, TB is spreading fastest in areas hardest hit by HIV/AIDS—sub-Saharan Africa and Eastern Europe. Between 1990 and 2004, TB incidence in Africa more than doubled, from 153 cases to 356 cases per 100,000 people. In the former Soviet bloc countries of Eastern Europe, TB incidence per capita rose through the 1990s, but has eased since 2001. Incidence rates may still be increasing in some Central Asian republics such as Tajikistan and Uzbekistan.[3]

What Makes TB So Deadly?

The bacteria that cause TB usually attack the lungs, but can spread to other parts of the body. Symptoms may include fever, cough, night sweats, weight loss, fatigue, and coughing up blood.

Most people infected with TB bacilli will not become sick. The immune system may wall off the TB bacilli in a thick waxy coat that allows them to lie dormant inside the body for decades. People with latent TB infection do not feel sick, do not have any symptoms, and cannot spread the disease. But, between 5 percent and 10 percent will develop TB in the future.[4]

TB spreads through the air, like the common cold. Only people who are sick with TB in their lungs or throat are infectious. People who have TB in other parts of their body are not infectious. When infectious people cough, sneeze, spit, or just talk, they propel TB bacilli, into the air, potentially infecting another person. Left untreated, each person with active TB in their lungs will infect between 10 and 15 people per year.[5]

HIV–TB Coinfection

HIV infection is a major risk factor for TB. HIV fuels the progress of TB by weakening a person's immune system. For someone already infected with TB, HIV can speed the progression to the active form of the disease and raise the chance of dying from TB. TB is also harder to diagnose in someone infected with HIV. Someone who is HIV-positive and infected with TB is 30 times more likely to become sick with TB than someone infected with TB who is HIV-negative.[6]

Much of the rise in TB incidence since 1980 is attributable to the spread of HIV in Africa. An estimated 13 percent of adults worldwide with newly diagnosed TB in 2004 were also infected with HIV. But in Africa, this rate reached 34 percent, compared with less than 1 percent in Bangladesh, China, Indonesia, and Pakistan. In Zimbabwe and South Africa, the TB-HIV coinfection rate exceeded 50 percent.[7]

TB is now the leading cause of death among HIV-positive adults living in less developed countries. It is responsible for 11 percent of all adult AIDS deaths worldwide. The TB burden in countries with a generalized HIV epidemic has increased rapidly over the 1990s, especially in the high-HIV-prevalence countries of eastern and southern Africa.[8]

A more coordinated and collaborative approach to TB and HIV control is needed to contain the spread of TB. Interactions between TB drugs and HIV drugs present a major new challenge: No proven simple regimen for simultaneous treatment exists.[9]

Treating TB

The Direct Observed Therapy Short Course, or DOTS approach, which is based on prompt diagnosis and effective treatment of individuals with smear-positive, or

infectious, TB to interrupt the transmission of TB is the foundation of plans to halt TB's march. DOTS consists of five components:

- Sustained political commitment with long-term planning and adequate human and financial resources;
- Case detection by sputum-smear microscopy in symptomatic patients;
- Standard short-course chemotherapy treatment given under direct observation;
- Adequate uninterrupted drug supply; and
- Systematic monitoring and accountability for every patient diagnosed.[10]

Community health workers deliver treatment and watch the patient take it to ensure compliance with the full regimen. A complete treatment can take six months to two years. One recommended regimen involves four drugs daily for the first two months, and two more drugs for another 18 weeks.[11] Unfortunately, when patients feel better after a short period of time, they often stop treatment and develop multidrug-resistant TB, which is harder to treat.

A six-month supply of drugs for DOTS costs less than US$25 in many parts of the world. Treatment was successful in an average of 82 percent of DOTS cases in 2003. In some areas, DOTS achieves cure rates of up to 95 percent, rates high enough to dramatically reduce the TB burden while preventing the emergence of drug-resistant TB.[12]

But the DOTS approach has its limitations. During the 1990s, the HIV epidemic brought into question whether DOTS was an adequate control strategy for sub-Saharan Africa. Even the most rigorous DOTS programs could not adequately compensate for the rising susceptibility to TB in populations with high HIV prevalence.

TB and HIV/AIDS programs have long operated independently. Indeed, less than 10 percent of TB patients in sub-Saharan Africa are even tested for HIV. Only recently have joint efforts begun to fight the two epidemics.[13]

Drug-Resistant TB

In 1944, streptomycin—the first antibiotic to effectively halt the progression of TB—became available. Other effective anti-TB drugs appeared in the following decade. But strains of TB resistant to all major anti-TB drugs have emerged. While single drugs often led to the rise of resistant forms of TB, researchers discovered that treatment with a combination of two or three drugs could be successful.[14]

Drug-resistant TB is caused by partial or inconsistent treatment, when patients do not take all their medicines regularly for the prescribed period, because they start to feel better, because doctors and health workers prescribe the wrong treatments, or because the drug supply is unreliable. A particularly dangerous form of drug-resistant TB is multidrug-resistant TB (MDR-TB), a form of the disease caused by TB bacilli that are resistant to the two most powerful anti-TB drugs. It is stronger, deadlier, and harder to treat than non-MDR-TB.

Unlike some illnesses where taking some drugs is better than doing nothing, poorly supervised or incomplete treatment of TB is worse than no treatment at all. People who take an antimicrobial drug too short a time, at too low a dose, or at too low a potency may remain infectious. The bacilli in their lungs may develop resistance to drugs that fight TB. And the people they infect will catch the same drug-resistant strain. Although drug-resistant TB is treatable, it requires up to two years of chemotherapy that is often prohibitively expensive and toxic to patients.[15] Drugs to treat one person for MDR-TB can cost up to 300 times the traditional treatment: US$50 vs. US$15,000).[16]

Three percent of all new TB cases that arise worldwide each year are estimated to be multidrug-resistant, but rates are much higher in some countries, especially in the former Soviet republics. More than 10 percent of new TB cases in Estonia, Latvia, and parts of Russia are multidrug-resistant. Economic decline, poor TB control and substandard health services since the break-up of the Soviet Union in 1991 are behind the rise of MDR-TB in Eastern Europe.[17]

When Health Systems Fail

TB is an opportunistic killer. In both rich and poor countries, TB thrives where health systems have collapsed. Cuts in government funding, haphazard health spending, and erratic drug supplies foster the spread of TB. Former Soviet republics are among the overburdened, underfunded health care systems that cannot ensure that patients will be properly treated with the best mix of the most effective drugs.

Looking Ahead

Although funding for drug development has increased, many tasks remain unfinished. Among them is the search for an effective vaccine to prevent TB—a "silver bullet" to finally conquer this ancient disease. But a TB vaccine has proved elusive. The Bacille Calmette-Guérin

(BCG) vaccine is widely used outside the United States to protect children against TB. The BCG vaccine's immunity wanes over time, and no vaccine protects adults against pulmonary TB.[18]

As of March 2006, four vaccines had completed phase I clinical trials, one of several steps in the long path to approval for general use. Most of these vaccines are responses to BCG's deficiencies, either as a booster for people previously vaccinated with BCG, or to confer longer-lasting immunity than conventional BCG.

The fight against TB also requires better accounting of the number of TB cases. Up to 60 percent of TB cases can be detected by existing diagnostic methods and nearly all can be cured with existing regimens. Yet case detection rates have fallen short of targets. In 1991, the World Health Assembly set a target to detect 70 percent of all infectious cases of TB by 2005. But only 45 percent of cases were detected. A goal to cure at least 85 percent of those cases was not met either; only 80 percent of known cases were successfully treated by 2005.[19]

Part of the challenge is ensuring proper diagnosis. There is no inexpensive and rapid way of diagnosing the disease. Sputum microscopy, the main diagnostic approach, has remained unchanged since the 1880s when it was first developed. It detects roughly half of all active cases of TB, but takes multiple examinations and may take days to complete—during which patients drop out of the process. It cannot detect smear-negative, or noninfectious disease. Nor can it diagnose pediatric and multidrug-resistant TB.[20]

Improving Treatment Options

More than half a century after the introduction of effective chemotherapy for TB, the disease remains unconquered and in some poor countries with high HIV rates, unstable.[21] While multidrug regimens can cure 95 percent of patients with active, drug-sensitive pulmonary TB, new and better drugs are needed, especially drugs that could reduce the standard six-month treatment regimens.

Treatments for multidrug-resistant TB must also be improved. They are fairly ineffective, expensive, poorly tolerated, and must be taken for up to two years, which discourages patients from sticking to the regimen. Treatment regimens that can be used safely simultaneously with commonly prescribed therapies for HIV are also a research priority.

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Special Section: The Next Pandemic

by Sandra Yin

As microbes continue to evolve, new infectious diseases and more virulent strains of current diseases will emerge. Some may generate deadly pandemics. Indeed, future epidemics may be inevitable, but a timely response by public health systems can limit their effects. The recent HIV and severe acute respiratory syndrome (SARS) epidemics—and the specter of horrific epidemics of the past—have focused attention on the need to detect emerging epidemics in time to limit their spread.[1]

New pathogens appear with alarming frequency—about one per year. The task of identifying these new pathogens calls for more collaboration among scientists who may be more used to working independently and competing with each other. Collaboration could mean the difference between years of guesswork and protracted patent battles vs. more efficient detection in which researchers share breaking news, test competing theories, and find answers in a matter of weeks or months.

After watching the long patent battle over the AIDS test two decades ago, a team of researchers in Hong Kong decided to donate the virus behind SARS to all interested laboratories. Ultimately, the joint efforts of many labs helped scientific sleuths identify the SARS virus a little more than a month after signs of a deadly atypical pneumonia first emerged in southern China in early 2003.[2]

Researchers are always on the lookout for the next new infectious disease. Health officials have been monitoring a new and extremely pathogenic virus—the avian influenza A (H5N1)—since it first infected humans in Hong Kong in 1997. By June 2006, 224 cases from 10 countries had been reported to the World Health Organization (WHO). Of those, 127 resulted in death.

While it's likely that only the patients with the worst cases go to clinics and are counted, the high fatality rate among reported cases of H5N1 has raised the question: Will the H5N1 bird flu virus be the source of a new flu pandemic?

No one knows for sure. The H5N1 flu virus does resemble the deadliest influenza virus of the 20th century, the 1918 virus, which may have started out as an avian flu virus.[3] And certain genes in the 1918 flu that allowed it to replicate efficiently in human bronchial cells are similar to genes found in H5N1.[4]

Officials fear that the bird flu virus, which has already spread from Asia to Europe, could mix with a strain of human flu and spawn a deadly virus that passes from person to person as easily as the common cold. For now, it is a bird virus. It does not yet and may never spread easily among humans.[5]

Unfortunately, our ability to detect new viruses is limited by our surveillance system. And the power of a global detection system relies on local labs and to be on the lookout for unfamiliar pathogens. What happens at the local level very much affects global surveillance efforts. But only 83 countries participate in WHO's global influenza surveillance system.

Past influenza epidemics have given warning signs of their arrival months or even a year before cresting, but usually are identified only in retrospect. In 1918, a "herald" wave caused substantial deaths at least six months before the major force of the epidemic hit in September of that year. The 1968 pandemic smoldered in Europe in its first season and pandemic deaths didn't peak until a full year after the pandemic strain arrived. In the 1957 pandemic worldwide and the 1968 pandemic in North America, most of the excess deaths attributed to the pandemic occurred in smaller waves in subsequent years.

If the next pandemic follows the 20th century pattern, it may do most of its damage after its first season. Herald waves or smoldering activity as a pandemic virus gradually emerges in its first season may give drug companies more than a few months' breathing space to produce and distribute vaccines and antivirals.

A stronger surveillance system would help researchers detect the earliest possible warning signs that an infectious strain has begun to spread. Public health measures could then be quickly initiated, including an emergency program to produce massive amounts of vaccine. While reducing the impact of the first wave of infections may be difficult, it might be possible to lessen later waves.

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