For a few exhilarating decades in the middle of the twentieth century, it seemed the world might have a reprieve from some major infectious diseases. After coordinated worldwide efforts had virtually eliminated smallpox and made major inroads against other infectious diseases such as influenza, tuberculosis, and polio, some public health officials thought we had entered a new era in which infectious diseases would no longer be among the planet’s worst killers. By the 1980s, though, those hopes were dashed, due in large part to the burgeoning AIDS epidemic.

Beginning around the same time, dozens of other infectious diseases—including Lyme disease, hantavirus pulmonary syndrome, West Nile virus, and Ebola hemorrhagic fever—were either newly recognized, spread to new locations, or became increasingly deadly. In 2003 alone, SARS, avian influenza, and monkeypox were among the infectious news makers. Along with the “new” diseases, long-time threats such as malaria surged back, now killing about 3 million people each year and infecting at least 300 million more, according to the 2002 U.S. National Institute of Allergy and Infectious Diseases (NIAID) publication *Microbes: In Sickness and in Health*.

More than a dozen major factors have been pegged over the past 10–15 years as existing or potential contributors to infectious disease outbreaks. Microbes continue to evolve rapidly, and
human susceptibility to infection is increasing due to malnutrition, weakening of immune systems through cancer treatments or chronic diseases, and aging of the population in some countries. Extensive poverty and population growth have spawned impacts such as poor basic public health infrastructure in megacities. Wars result in dislocation of peoples, destruction of public health systems, malnutrition, and introduction of new microbes by soldiers returning home; bioterrorism raises the possibility of infectious agents being released upon the population at large. Changing medical technology allows exchanges of microbes through blood transfusions and organ and tissue transplants, some of which come from animals. Increased international travel and exchange of goods—including animals, plants, and foods that can carry pathogens—both spread diseases rapidly. Many nations have seen reduced funding for safe water and sewer systems, vaccines, research, surveillance, prevention, and response, due in part to complacency.

As if those driving forces weren't enough to contend with, many environmental factors are playing major roles, including climate change, deforestation, global dust transport, and numerous agricultural practices. The links between these factors and millions of potential human deaths have often been overlooked or discounted as pollution and other more obvious concerns have typically drawn the limelight.

Emerging and Surging

The complex relationship between people and microbes has been evolving for tens of thousands of years. Many microbes are essential to our health. But a few bacteria and many viruses, fungi, and protozoa can cause infectious diseases and play a role in cancers, coronary heart disease, diabetes, multiple sclerosis, autism, and chronic lung diseases.

With the accelerated development of vaccines and antibiotics in the past century, along with major regional and worldwide drives to use these new tools, some of the worst offenders have been beaten back. Smallpox, for example, which some researchers say at one time had killed more people than all other infectious diseases combined, was virtually eliminated in 1977 thanks to a global vaccination effort. Along with the success against smallpox came strides against polio, malaria, measles, guinea worm disease, and other nemeses.

More than 1,400 species of infectious microbes are known to be human pathogens, and of these, 175 fall into the "emerging" category, wrote Louise H. Taylor and colleagues from the U.K. Centre for Tropical Veterinary Medicine in the 29 July 2001 issue of Philosophical Transactions: Biological Sciences. Of the total 1,400-plus species, 61% are zoonotic, meaning they can be passed from animals to people, and about 75% of the emerging species are zoonotic. Viruses and protozoa are among the most likely to be considered "emerging."

Stephanie Schrag, an epidemiologist with the Centers for Disease Control and Prevention (CDC), says estimates of the number of emerging infectious diseases can vary because there's no universal agreement on exactly what constitutes an emerging or re-emerging disease. In general, emergence has been tied to substantial increases in mortality and morbidity, but there are no strict thresholds for when a disease is considered emerging, and problems around the world with data quality compound the problem. However, Schrag says, a precise number isn't the most important issue. "It only takes one [outbreak] to have a serious global problem," she says.

Costly Killers

In the United States, efforts against infectious disease have led to huge reductions in resulting deaths, with rates in 1980 less than 5% what they were in 1900, according to an analysis published by Gregory Armstrong and colleagues from the CDC in the 6 January 1999 Journal of the American Medical Association. Other developed countries have seen similar progress, and some developing nations have had sporadic successes.

The downside of that progress has been widespread complacency, says Randall Culpepper, director of overseas operations for the U.S. Department of Defense's Global Emerging Infections Surveillance and Response System. Although some such relaxed vigilance is evident on the part of health workers and the public, perhaps most important has been complacency among politicians who fund public health efforts. As a result, funding for a variety of
public health programs was cut starting in the 1980s, disease surveillance was reduced, and efforts shifted toward chronic diseases such as cancer—although the U.S. death rate for noninfectious diseases has barely nuded downward since 1900.

Microbes needed only a few years to find windows of vulnerability. Today, infectious diseases are once again a cause for grave concern, causing about one-quarter of the world’s 55 million deaths each year, according to the 1999 World Health Organization (WHO) report Removing Obstacles to Healthy Development. They trail only cardiovascular disease in terms of causing death, and are responsible for twice as many deaths as cancers. About 90% of infectious disease deaths are caused by acute respiratory infections (such as influenza and pneumonia), diarrheal diseases, tuberculosis, malaria, measles, hepatitis B, and HIV/AIDS. More than 40 million people have been infected with HIV worldwide, for example; more than 20 million people have died of HIV/AIDS in just 20 years, and another 45 million are expected to become infected by 2010, according to the WHO. Various estimates put AIDS as the second to fourth leading cause of death worldwide.

In developed countries, the percentages of infectious disease deaths tend to be much lower than the average, though they too have risen in the past few decades. In the United States the rate has approximately doubled since 1980, to about 170,000 people per year, said the U.S. Central Intelligence Agency’s National Intelligence Council (NIC) in a 2000 report, The Global Infectious Disease Threat and Its Implications for the United States.

Costs from infectious diseases can be substantial worldwide. The 2003 SARS outbreak cost China and Canada about 1% of their economies, primarily through lost tourism and travel revenues, the NIC reported in the August 2003 publication SARS: Down But Still a Threat. In sub-Saharan Africa, workforce havoc wrought by HIV/AIDS and malaria alone are expected to reduce gross domestic product by 20% or more by 2010, the NIC reported in Global Infectious Disease Threat. In the United Kingdom, cases of bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease in 1995 led to mass cattle slaughters and a three-year beef embargo, costing the British economy US$5.75 billion. Even the relatively low number of U.S. infectious disease cases costs more than $120 billion per year to treat, noted the NIAID in Microbes: In Sickness and in Health.

Conversely, prevention can be cost-effective. Eradication of smallpox reduced the global health bill by $20 billion, and the $3 billion savings in the United States cost a relatively paltry $32 million in preventive measure investments, the CDC said in its 2002 report, Protecting the Nation’s Health in an Era of Globalization: CDC’s Global Infectious Disease Strategy.

Beyond the lives lost and dollars spent, infectious diseases have a number of other costs, such as the breakdown of social structure. According to the Joint United Nations Programme on HIV/AIDS, 14 million children had lost one or both parents to HIV/AIDS by the end of 2001, and the NIC said in Global Infectious Disease Threat that number will reach 42 million by 2010.

Emerging Environmental Factors

Many infectious disease deaths are linked with environmental factors. The environmental factor that affects perhaps the most countries is climate change. Some infectious diseases may change in tandem with climate; among the primary suspects, based on piecemeal evidence, are malaria, dengue fever, cholera, and yellow fever. But extensive, long-term evidence is scant so far. “It’s very difficult to attribute disease change to climate change,” cautions Jonathan Patz, director of the Program on Health Effects of Global Environmental Change at the Johns Hopkins Bloomberg School of Public Health. Usually there are at best only weak long-term health data on potentially pertinent diseases, and many confounding factors—such as changes in pest control practices, travel patterns, and human settlement densities and locations—make analysis more difficult.

One significant exception to date, Patz notes, is a linkage between cholera and the El Niño/Southern Oscillation (ENSO). In Bangladesh from 1893 to 2001, as described by physical scientist Xavier Rodó of the University of Barcelona and colleagues in the 1 October 2002 Proceedings of the National Academy of Sciences. The team found that ENSO, which causes warmer-than-usual equatorial Pacific Ocean temperatures, was responsible for more than 70% of the variance in cholera mortality and morbidity, and that ENSO was increasing in both frequency and intensity over time, possibly in connection with long-term ocean warming trends.

According to the 2003 WHO publication Climate Change and Human Health: Risks and Responses, other clues are offered by shorter-term evidence, such as links in New Zealand between temperature rise and salmonella infections, in the South Pacific between La Niña and cholera mortality and morbidity, and in many climates between rainfall and diarrheal diseases such as shigellosis and cryptosporidiosis. The WHO concluded that climate change may play a relatively small but nonetheless very real role in the world’s death totals, already killing more than 150,000 people per year, in part through increases in infectious diseases.

While much science remains to be done, “climate stability is a crucial issue for all aspects of society,” says Paul Epstein, associate director of the Center for Health and the Global Environment at Harvard Medical School. “If we don’t get the solutions right, all the other issues are moot.”

Climate culprit. Long-term warming trends have been shown to encourage the spread and worsen the impact of some infectious diseases.
Another globe-encompassing factor is the intercontinental transport of dust, which arises from at least 10 major soil reservoirs on five continents, according to EHP’s February 2002 Focus article (EHP 110:A80–A87 [2002]). In the 19 March 2003 Geophysical Research Letters, scientists funded by the U.S. National Aeronautics and Space Administration documented some of the farthest transport yet, confirming that dust in the French Alps had floated from China during a two-week journey in 1990.

Hundreds of millions of tons of dust circle the world each year, wrote researchers from the U.S. Geological Survey (USGS), Florida International University, the University of South Carolina, and the company Microgenomics in the May 2003 issue of BioScience. And just 1 million tons of dust may contain 10 quadrillion microbes, the USGS noted in its January 2003 publication African Dust Carries Microbes Across the Ocean: Are They Affecting Human and Ecosystem Health? Many microbes are killed in transport, but far more than expected survive, researchers have found.

Microbes in airborne dust known to be pathogenic to people include those causing plague, anthrax, tuberculosis, influenza, hantavirus pulmonary syndrome, meningococcal meningitis, coccidioidomycosis, and aspergillosis. However, as yet there are no proven links between airborne dust and infectious disease outbreaks in people, says Christina Kellogg, a USGS research microbiologist who contributed to the BioScience paper.

At the local scale, land use changes triggered as the world’s population rockets past 6.3 billion (up from 4 billion just 30 years ago) are influencing infectious diseases. Urbanization, road and dam construction, deforestation, forest fires, and pollution can all play a role in diseases such as Lyme disease, leishmaniasis, dengue fever, and schistosomiasis.

Lyme disease, caused by the bacterium *Borrelia burgdorferi* and transmitted by ticks from wildlife to people, was first observed in 1977 in Connecticut. The generally nonfatal disease can be very painful, causing symptoms such as joint and muscle pain, headache, fatigue, fever, sleep disorders, and personality changes.

One important contributing factor to Lyme disease emergence is fragmentation of forest habitat, says Richard Ostfeld, an animal ecologist with the Millbrook, New York–based Institute of Ecosystem Studies. In an article published in the February 2003 issue of Conservation Biology, he and his team found that important Northeastern tick host species such as white-footed mice fared better when forest tracts were smaller than five acres, and that the infection rate of ticks was much higher in the small tracts. When people lived next to these tracts, the odds of human infection rose substantially.

In another study, published 21 January 2003 in Proceedings of the National Academy of Sciences, Ostfeld and his team confirmed that tick infection rates were generally linked with species diversity—the more species in a tract, the lower the overall tick infection rate. In their research tracts in southeastern New York, they found that it was most important to retain squirrels and opossums, which can clear the infection quickly and don’t pass it on to other ticks. On the other hand, shrews and white-footed mice proved to be very important disease carriers.

Humans play many other roles in transmitting disease to humans as well. “Humans are horribly susceptible to a wide range of diseases from many animals,” says William Karesh, head of the Wildlife Conservation Society’s Field Veterinary Program. Recent examples of diseases either proven or strongly suspected of originating with animals include HIV/AIDS, simian immunodeficiency virus, SARS, monkeypox, and Ebola hemorrhagic fever.
The huge surge in international trade of animals for uses such as pets or exotic cuisine may be the biggest concern from a global perspective, Karesh says, because diseases can be transported so rapidly and widely. In the United States alone, such trade has grown 62% in the past decade, sparked in large part by the increase in disposable income in the United States, as well as easier travel, transport, and electronic payment methods.

This trade now involves 352,000 species. U.S. Fish and Wildlife Service (FWS) deputy director Marshall Jones told a Senate committee on 17 July 2003. Jones testified that the 2002 U.S. traffic in live animals included 216 million fish, 49 million amphibians, 2 million reptiles, 365,000 birds, and 38,000 mammals. The CDC has found that potentially fatal diseases such as monkeypox, salmonellosis, tularemia, and plague have been transmitted to people via imported animals such as squirrels, mice, lizards, snakes, and turtles.

FWS inspectors attempt to monitor this animal traffic, but with just 92 of them at 32 points of entry into the country, they would have approximately three seconds to inspect each animal if that’s all they did every minute of every work day. And they are not trained to detect diseases, but rather to look out for endangered species and ensure that animals are being transported safely.

The responsibility for controlling this traffic isn’t solely that of the FWS; the U.S. Department of Agriculture, the U.S. Food and Drug Administration, and the CDC also have roles. Mira Leslie, a public health veterinarian with the Washington State Department of Health, says progress is being made incrementally, as shown by the response to a July 2003 position statement by the Council of State and Territorial Epidemiologists to have these agencies, along with the National Association of State Public Health Veterinarians, jointly develop policies to regulate this traffic. New regulations to control monkeypox have been implemented with unprecedented speed, but so far a more comprehensive multiagency prevention and control plan has not been developed, Leslie says.

Local consumption of indigenous animals also can cause major problems, though possibly more slowly. HIV/AIDS, thought to have first been acquired from animals about a half a century ago, has taken decades to wreak its havoc. But with the speed of travel now possible, many observers fear that other diseases may take hold similarly, but much more quickly. SARS (suspected of being transmitted from animals such as civet cats and ferret badgers) and diseases strongly suspected to be common to both people and some primates (including Ebola hemorrhagic fever and simian immunodeficiency virus) are examples of those that worry many public health officials.

Domestic animals also can play a role in the spread of infectious diseases. The pathogenic bacterium *Escherichia coli* O157:H7, first recognized as a cause of illness in 1982, is clearly associated with cattle, says Sheridan Haack, a USGS research hydrologist studying the microbe, citing evidence accumulated over the past two decades. "Farmers who handle cattle, or others who encounter cattle on a regular basis, are at greater risk of acquiring the disease," she says. Also at risk are people who eat inadequately cooked infected beef, which typically includes about 25–40% of the animals sampled in feedlots, according to a University of Nebraska study in the 2 January 2004 issue of *Vaccine* (although tests with vaccines and beneficial bacteria show those numbers can be cut by two-thirds). About 10–15% of people affected develop complications that can lead to kidney failure and death.

The construction of irrigation dams has been linked with the spread of other diseases. In a number of locations around the world, such dams have increased the breeding habitat for mosquitoes, resulting in large increases in malaria over relatively short periods of time, Patz says. For example, a presentation at the 2002 colloquium Unhealthy Landscapes: How Land Use Change Affects Health, sponsored by the WHO, the United Nations Environment Programme, the NIH John E. Fogarty International Center, and the NIEHS, cited a sevenfold increase in Ethiopia following dam construction. (These proceedings have been submitted for publication in *EHP*.)

We are what we eat. Diseases such as SARS are suspected of being transmitted to people through consumption of indigenous animal meat such as the goods sold in this market in Guangdong Province, China.
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Dam building in Africa has also created habitats that contribute to increased mosquito and snail populations and resulting outbreaks of Rift Valley fever and schistosomiasis, respectively, the NIC said in Global Infectious Disease Threat. Other agricultural practices can play a role in the spread of infectious diseases. The widespread use of antibiotics in animals is of worldwide concern because of the role such uses can play in the surge in antibiotic resistance. The Institute of Medicine (IOM) recommended in its 2003 report Microbial Threats to Health: Emergence, Detection, and Response that the Food and Drug Administration should ban uses of antibiotics for growth promotion in animals for any drug classes also used in people. In the same report, the IOM warned that many emerging infectious diseases are linked with changing land use practices. One of those practices is the spread of sewage sludge and its associated pathogens. In the United States, the Environmental Protection Agency’s standards for treated sewage sludge are seriously outdated and don’t adequately address health concerns, asserted the National Research Council in the 2 July 2002 report Biosolids Applied to Land: Advancing Standards and Practices. The IOM also cautioned that infectious diseases are linked with “ecological changes that can alter the replication and transmission patterns of pathogens.” One practice that can substantially alter ecosystems is the widespread use of hundreds of millions of pounds of pesticide products. On the other hand, the IOM recommended the use of some pesticides to control disease vectors.

Defensive Tactics

With threats from infectious diseases accelerated by so many factors, it’s impossible to intervene quickly on all fronts. But some experts have ideas about a few overarching concepts to consider.

In an article in the 1998 book Pathology of Emerging Infections 2, Johns Hopkins international health professor Donald Burke wrote that RNA viruses may be one of the biggest concerns, because they can mutate, recombine, and cross between species so rapidly. Influenza, polio, HIV/AIDS, and foot- and-mouth disease are caused by RNA viruses. The research to date on SARS indicates that it may be caused by two types of viruses that Burke predicted would be of great concern: coronaviruses and reoviruses. The coronavirus may have come from an extremely rare recombination of viruses from mammal and bird hosts, wrote David Guttman, a University of Toronto professor of evolutionary genomics, in the January 2004 issue of the Journal of Virology.

Schrag agrees that RNA viruses are a serious threat. Influenza, for example, has killed and continues to kill huge numbers of people, including 20–40 million people in 1918–1919. In recent years, about 3.5 million people have died annually from acute respiratory infections, including influenza and pneumonia. Influenza deaths surge in fairly regular cycles. For instance, there were about 70,000 U.S. deaths in 1957, about 34,000 in 1968 (when the average was then about 20,000), and about 65,000 in 1999. The current average is about 36,000, which some public health officials fear will be greatly exceeded in 2004, due to the early and strong onset of a strain called A/Fujian, which isn’t fully protected for with the current vaccine. A full pandemic might kill 89,000–207,000 people in the United States, wrote Maine state epidemiologist Kathleen Gensheimer and colleagues in the December 2003 issue of Emerging Infectious Diseases.

Karesh has a little different take. He suspects that the greatest threats may come from those microbes that are generalists—thriving in many settings and species—because they are so widespread and so adaptable to a range of conditions. The microbes that cause tuberculosis, Nipah virus encephalitis, rabies, salmonellosis, herpes, and hantavirus pulmonary syndrome fall under that umbrella.

Patz says that it may be best to focus on diseases that are being promoted by human activity and that are therefore preventable. In that light, issues such as land use changes, global warming, and international travel and shipping may be very important.

As agencies worldwide struggle to cope with infectious diseases, many have begun

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Making microbes meaner. Practices such as insecticide spraying can lead to microbial resistance.

It’s a small world after all. Burgeoning global travel means that infectious disease outbreaks are more likely to become a global—rather than local—phenomenon.
piecemeal efforts to address some of the threats, spending billions of dollars on surveillance, mitigation, and treatment of specific diseases in the past few years alone. The WHO established its Global Outbreak Alert and Response Network in 2000, drawing together basic information on a handful of key infectious diseases (though the agency is limited in what it can do in response to outbreaks when they occur). The SARS outbreak in 2003 led to better coordination among many of the world’s agencies.

And disease control efforts have sometimes shown multiple benefits. For instance, the slaughter and management of farm animals in southern Scotland in 2001 in response to a foot-and-mouth disease outbreak led in turn to reduced human cases of cryptosporidiosis, also linked with farm animals, Norval J.C. Strachan of the University of Aberdeen and colleagues reported in the 1 September 2003 Journal of Infectious Diseases.

In other signs of progress, the fourth International Conference on Emerging Infectious Diseases, beginning 29 February 2004 in Atlanta, likely will expand understanding of infectious disease issues. A number of agencies in the United States are beginning to talk to each other a little more, breaking down old bureaucratic and turf barriers, Karesh says. The CDC is in the midst of updating its strategic plan for coping with emerging infectious diseases, and researchers at agencies such as the Environmental Protection Agency and the Department of Agriculture are developing models to predict outbreaks of illnesses such as Lyme disease. Other researchers, funded through the Ecology of Infectious Diseases initiative sponsored by the National Science Foundation, the NIH, and the USGS, are investigating numerous links between human diseases and the environment.

Bans on some of the agencies dealing with infectious diseases have risen dramatically over the past decade. For instance, the CDC’s National Center for Infectious Diseases has seen its emerging infectious diseases national plan implementation budget leap from $1 million in 1994 to about $164 million in 2002. But this budget plateaued in 2003 and is expected to drop slightly in 2004. And spending of hundreds of millions of dollars by agencies such as the NIAID to fight perceived bioterrorism threats such as smallpox barely addresses the wide range of potential causes of natural outbreaks, says Epstein.

Efforts so far are indeed limited and too disease-specific, says Mark S. Smolinski, study director for the IOM’s Microbial Threats to Health and now a senior program officer with the Nuclear Threat Initiative, a privately funded advocacy organization. “There’s no master plan,” he says. “It’s still surprising to me that agencies within a single department really don’t know what each other is doing. There is no research agenda in the United States for infectious disease.” Just establishing an effective global surveillance network is at least a decade or more away, the NIC said in Global Infectious Disease Threat.

But even with careful observation, diseases caused by naturally occurring microbes can be difficult to spot until large outbreaks occur, because identifying a true outbreak amongst all the background noise of other diseases requires an ideal confluence of very observant medical personnel, a highly effective reporting network, and diligent data analysts. And synthetic microbes, which now can be created in a matter of weeks, add to the potential for outbreaks if they escape from their laboratories by accident or by design. Furthermore, identifying outbreaks doesn’t always help. Some countries don’t report them, for economic, cultural, religious, or political reasons, as when China initially withheld information about SARS from the world for several months after the disease first appeared. And the difficulty of enforcing quarantines in relatively open societies contributes to problems in controlling outbreaks once they are discovered.

In addition, the medical tools needed to fight outbreaks are limited. Vaccines often take years to develop, and many antibiotics are no longer effective, due to resistance developed by microbes. For example, part of the reason for the surge in malaria cases is increasing resistance to drugs used to treat it. In sub-Saharan Africa, infection rates increased by 40% from 1970 to 1997, the NIC reported in Global Infectious Disease Threat, and in 80 of the 92 countries heavily affected by malaria, the first-line drug treatment, chloroquine, no longer works. Alternatives can cost up to 33 times as much as chloroquine [see “An Affordable Antimalarial,” p. A25 this issue], and some can have more side effects, take longer to cure, and entail protocols that are more difficult for patients to comply with.

When outbreaks do occur, even countries with the most advanced medical facilities remain ill-prepared to handle them. Canada did well coping with its 2003 SARS outbreak, but still the episode “completely overwhelmed their medical system,” Smolinski says. In the United States, the medical system would break down under similar pressures, the U.S. General Accounting Office has said in several 2003 reports.

Those pressures likely will continue to surface around the world—and sooner or later they will surface in the United States. “One can safely predict that infectious diseases will continue to emerge, and that we will encounter unpleasant surprises, as well as increases in already worrisome trends,” the IOM concluded in Microbial Threats to Health. “Depending on present policies and actions, this situation could lead to a catastrophic storm of microbial threats.”

Although some steps are being taken to fight emerging and re-emerging infectious diseases, it likely will be a decade or more before any substantial global structure for coping with infectious diseases is in place, said the NIC in Global Infectious Disease Threat. In the interim and possibly beyond, the NIC speculated, microbes will continue their deadly hot streak.

Bob Weinhold