New and Reemerging Infectious Diseases: A Global Crisis and Immediate Threat to the Nation’s Health

The Role of Research
Basic and clinical research programs in academic, government, and industrial laboratories play a pivotal role in understanding infectious diseases. Increasingly, it is possible to identify new pathogenic, or disease producing, microbes, define their transmission, and develop methods to control them. We have come a long way in controlling some of the infectious scourges of history and solving former mysteries of human health. Just a short time ago, who would have believed that ulcers, long thought to be caused by the stresses of daily living, were caused by a bacterium and could be controlled by the judicious use of antibiotics? Who would have known that showers could harbor the agent of Legionnaires’ disease, which poses a particular risk to older individuals? And who would have dreamed that the most common cause of childhood meningitis could be successfully controlled or even eradicated?

But the war against pathogenic microorganisms is far from over. We live in a restless equilibrium and share the planet with countless microscopic creatures. Many recent health crises in the United States have been infectious in origin. The emergence of Lyme disease, hantavirus infection, foodborne Escherichia coli O157:H7 infection, and, of course, human immunodeficiency virus (HIV) infection has challenged our society on many levels and has caused concern, even panic in the population. Moreover, many infections like tuberculosis, dengue, and malaria are “enjoying” a renaissance of reemergence. The problem is compounded by an alarming increase in bacterial resistance to antibiotics, so that diseases caused by some microbes, such as some of those responsible for bacterial pneumonia and middle ear infection, are more difficult to treat. We pay for this in the cost of treatment, as well as in an increase in morbidity and mortality of those who are most vulnerable to these infections: children, the elderly and those with compromised immune systems. Clearly we must find new ways to detect, treat, and control infectious diseases. This requires entirely new approaches as well as modification and enhancement of proven approaches.

About the American Society for Microbiology
The American Society for Microbiology (ASM) is the largest single life science society, composed of over 42,000 scientists, teachers, physicians, and health professionals. The ASM’s mission is to promote research and research training in the microbiological sciences and to assist communication between scientists, policy makers, and the public to improve health, economic well-being, and the environment. The ASM and its members work to identify and support research efforts that can appropriately address infectious diseases. The goal of this booklet is to provide background information on the problem and to emphasize the critical role of research in responding to the global crisis and to the immediate threat to the nation’s health represented by new and reemerging infectious diseases.

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We stand on the brink of a global crisis in infectious diseases.
No country is safe from them. No country can any longer afford to ignore their threat.


It is time to strengthen our research efforts . . . so that we can unlock the mysteries behind antibiotic resistance and discover new scientific weapons in the battle to detect and control emerging infectious diseases.

— Vice President of the United States
Al Gore, June 1996
Diseases of Heart
Malignant Neoplasms
Infectious Diseases
Cerebrovascular Disease
Chronic Obstructive Pulmonary Disease
Accidents

1992 Deaths, %

Infectious diseases remain the leading cause of death worldwide. Seventeen million (32 percent) of the 52 million people who die each year succumb to infectious disease or complications arising from infection. This toll is not restricted to the developing nations of the world. Few realize that in 1996, infectious diseases in the United States ranked as the third leading cause of death. Five of the ten top causes of death in 1996 were related directly or indirectly to infectious diseases (pneumonia, acquired immunodeficiency syndrome (AIDS), chronic liver disease, chronic obstructive lung disease, and immunosuppression related to cancer chemotherapy). Data presented in the Journal of the American Medical Association (275: 189-193, 1996) indicate that the death rate from infectious diseases in the United States has increased more than 50 percent since 1980. Trends in death due to respiratory tract infections, HIV, and bloodstream infections, account for most of these increases.
It is estimated that as many as 9,000 people in the United States die annually from foodborne illnesses and 6.5 to 33 million illnesses in the United States each year are related to food—a number unheard of for a developed country. In 1993, the largest (>400,000 cases of diarrhea due to Cryptosporidium sp) waterborne disease outbreak in the U.S. history occurred. An outbreak of acute, fatal respiratory distress syndrome in the Southwestern United States was shown to be due to hantavirus, a newly identified virus spread to humans in the feces and urine of the deer mouse. Initially thought to be limited to the Southwest, it appears that the deer mouse is one of the most common rodents in the country and fatal hantavirus cases have been reported as far away as Miami and New York. The virus is now known to be carried by other rodents as well and another strain of the virus has been identified. In 1994, 1995, and 1996, locally acquired cases of malaria have been reported in the United States, where the disease has been nonexistent for 50 years. The appearance of dengue fever in the United States, the marked increase of Lyme disease, and the reemergence of tuberculosis and rabies are just a few examples of the rising tide of infectious diseases.
The threat from new and reemerging infections is compounded by an alarming increase in antibiotic resistant bacteria.

Antibiotics are now the most commonly prescribed category of drugs. Yet the efficacy of these miracle drugs is threatened by an alarming increase in antibiotic resistant bacteria. Although defining the precise public health risk of antibiotic resistance is not a simple undertaking, there is little doubt the problem is global in scope and very serious. Today more than 90 percent of the strains of Staphylococcus aureus are resistant to penicillin and other related antibiotics. This common bacterium causes a range of infections such as boils, toxic shock syndrome, and serious diseases of the lung, heart, and bone.

Enterococci (a kind of streptococcus) are the most common cause of hospital-acquired infections. The antibiotic, vancomycin, is often the last weapon available to treat these potentially deadly microbes. According to the U.S. Centers for Disease Control and Prevention, the incidence of vancomycin resistant enterococci in the United States increased 20 times from 1989 to 1993.

One of the miracles of modern medicine has been our ability to successfully treat bacterial pneumonia with penicillin. Before 1987, antibiotic-resistant Streptococcus pneumoniae (pneumococci) were uncommon in the United States. Recent reports indicate that in some parts of the country as many as 40 percent of strains of pneumococci are resistant to penicillin and other antibiotics. These bacteria are a leading cause of deadly bloodstream infections, pneumonia, and meningitis in the elderly and are one of the most common causes of middle ear and sinus infections in children.
Infectious diseases account for major health care expenditures in the United States

Infectious diseases account for 25 percent of all visits to physicians in the United States. Middle ear infections in children are one of the most common reasons for emergency room visits. Approximately $120 billion, or 15 percent, of all 1992 health care expenditures in the United States were related to direct or indirect costs of infectious diseases.

The annual financial cost of common infectious diseases in the United States is estimated by the National Science and Technology Council and the National Institutes of Health as follows:

- **Intestinal infections**: $23 billion in medical costs and lost productivity
- **Foodborne diseases**: $5 to 6 billion in medical costs and lost productivity
- **Sexually transmitted diseases**: $5 billion in treatment costs (excluding AIDS)
- **AIDS**: at over $10 billion in costs annually now the leading cause of death among adults aged 25 to 44
- **Hepatitis B virus infection**: Over $720 million in combined direct and indirect costs
- **Influenza**: $17 billion in medical costs and lost productivity
- **Otitis media (ear infection)**: over $1 billion in medical costs
- **Antibiotic resistant bacterial infections**: $4 billion in medical costs
How can we find ourselves in this predicament when in 1967, the surgeon general declared that the United States was ready to “close the book on infectious disease...” His optimism was based on the development of more than 25,000 antibiotic products by 1965. This coupled with the impressive effects of the pertussis and diphtheria vaccines led to the belief that bacterial diseases were no longer of great concern to physicians. Furthermore, polio and smallpox virtually had been conquered in the United States with vaccines. However, at this time little was known about the relatively new fields of virology, immunology, microbial genetics and microbial evolution. The remarkable capability of bacteria for developing resistance to antibiotics and the uncanny ability of microbes for environmental adaptation were only beginning to be imagined, much less be understood. While poverty and overcrowding of humans were known to enhance spread of infectious diseases, little was known about other factors involved in disease ecology and emergence of new and reemergence of old infectious agents once thought to have been controlled.

The 1992 Institute of Medicine’s (IOM) report entitled Emerging Infections: Microbial Threats to Health in the United States clearly articulates why we find the microbes winning the battle and how our previous optimism and complacency towards infectious diseases have weakened the ability of our public health infrastructure to either prevent or control microbial diseases. Furthermore, the report predicts that unless we dramatically alter our course that new and reemerging infectious diseases will increase the infectious disease burden in this country. The report identifies the following as major contributors to emerging microbial threats: changes in human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; microbial adaptation and change; and the breakdown of public health measures. A few specific examples follow.

**Demographics and Social Factors**

The most important message in the IOM report—often repeated but insufficiently heeded—is that infectious diseases that now affect people in other parts of the world represent real threats to the United States because of global interdependence, modern transportation, trade, and changing social and cultural patterns. The number of international airline passengers arriving in the United States increased from 2 million in 1950 to 280 million in 1990. The number of people from the United States traveling to developing countries continues to increase markedly. Microbes do not respect international boundaries. With international travel and a global economy being...
Lyme disease, transmitted by deer ticks, is the most common vector-borne disease in the United States, with 10,000 to 14,000 cases reported annually.

Overcrowding results in the rapid spread of infectious diseases. In 1990, the percentage of the population living in cities worldwide was less than 15 percent. Demographers predict that by 2010 50 percent of the world population will live in urban centers. Of particular relevance to the United States is the sharp rise in homelessness and the number of families sharing households and crowding into public housing.

Even children are at greater risk despite the successes of childhood immunization programs. The number of children in day care facilities has increased dramatically to more than 60 percent. This environment greatly increases the spread of respiratory and middle ear infections and diarrheal disease among children and their families.

Economic Development and Land Use

The way in which we use our land and other natural resources for economic development influences the incidence and type of infections people may acquire. Fungal spores universally are found in soil and lie dormant until disturbed; the more building that takes place, the greater the number of fungal meningitis and fungal pneumonia cases occur, particularly in the elderly and in immunocompromised patients.

The spread of Lyme disease, as well as rabies, is attributable, in part, to the increased number of people moving into rural and suburban areas to escape urban congestion. As we clear the land, we disrupt the predator-prey relationships that control deer populations, exposing people to deer and thus to deer ticks which spread Lyme disease. Rabies infected animals increasingly are found in suburban areas, forced into these populations because of loss of habitat. As a result, the number of rabies cases has doubled since 1987.
Combating infectious diseases requires a healthy research enterprise

Like the organisms themselves, the challenges of detecting and preventing infectious diseases are constantly evolving. A strong, stable research and training infrastructure is needed to investigate the mechanisms of molecular pathogenesis (cause of disease), the evolution of pathogenicity, drug resistance, and disease transmission. This fundamental knowledge is required in order to design new vaccines, discover new classes of antimicrobial compounds, and devise other novel means of preventing and treating infectious disease.

Basic research and discovery will provide the ultimate solutions to controlling infectious diseases. We realistically cannot eradicate all disease-producing bacteria, fungi, viruses, and other parasites, but it will be possible to control their spread and impact. At the same time, it is absolutely crucial to understand that life on this planet, including our own, requires coexistence with microorganisms. They affect not only our health but ultimately our sources of energy, our agricultural productivity, and our animal husbandry. Most of the facets of our existence depend to some extent on the microbial biosphere.

Thus in the long term, a sustained investment in all aspects of microbiology, immunology, and infectious diseases research will pay enormous dividends. In the near term our country requires an urgent, vigorous response to a counterattack by the agents of infectious disease. In reality, we are in a perpetual contest with infectious disease, one which requires an armamentarium of knowledge gained from basic research, surveillance, and improved health practices.

Research efforts should include a strong focus on the investigation of the molecular genetics and biochemistry of bacteria, viruses, and fungi. If the critical pathways and functions involved in microbial replication and development are understood, they can be targeted to develop novel antimicrobial drugs. With a better understanding of microbial physiology, research can help elucidate the mechanisms used by pathogens to develop antimicrobial resistance and perhaps devise ways to delay or even reverse the expression of these mechanisms.

Fundamental research provides the foundation for surveillance and response, and research training is vital for maintaining our capability to identify and control new diseases, both in the United States and abroad.

— Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, 1997.
of drug resistance by microorganisms. Basic studies that use gene sequencing technology are making it faster and easier to pinpoint and visualize the actual molecules in the pathways in microbial replication and development with the aim of better understanding their adaptability and host susceptibility. The complete chromosomal sequences of many of the most feared pathogens will likely become available over the next decade. With the proper research support and the knowledge we now have in hand, scientists can concentrate on understanding the differences between harmless and pathogenic microbes, differences that could mean life, disability, or death.

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) is the federal government's lead agency for funding scientific research on causes of infectious disease, pathogenic mechanisms, host defense mechanisms, vaccines, and antibiotics. In collaboration with other Public Health Service agencies and industry, NIAID sponsors basic and clinical research that yields multiple public health and economic benefits. NIAID’s focus on academic research and training complements its own research mission as well as the role of the Centers for Disease Control and Prevention, which has primary responsibility for surveillance and detection of emerging disease threats.
Increased research funding is critical to address the current threats from new and re-emerging infectious diseases through the development of better diagnostic tests, new drugs, and vaccines. In addition, increased funding would provide new opportunities for making major advances to define the potential role of infectious agents in chronic diseases, such as cancer, that currently have no known causes. Cancer is the second most common cause of death in many parts of the world. It generally is believed that environmental and lifestyle factors, as well as common practices such as diagnostic radiographic procedures, are responsible for this disease. The link between infectious diseases and cancer is becoming increasingly clear. According to the World Health Report 1996, up to 84 percent of some cancer cases worldwide are attributable to viruses, parasites, or bacteria.

- **Stomach cancer**—Approximately 550,000 new cases of stomach cancer per year are attributed to the bacterium *Helicobacter pylori*. First isolated from humans in 1982 (in university research supported by NIH funding), this bacterium has been shown to cause duodenal ulcers and gastritis. Although other factors are involved, infection with this bacterium has been shown to lead eventually to the development of stomach cancer. More research is needed to develop effective therapy and vaccines to prevent *H. pylori* infections and to understand its role in cancer.

- **Cervical cancer**—Human papilloma virus infection, a sexually transmitted infection of the cervix, involves a very high risk of developing cervical cancer. The infection is most prevalent in sexually active young adults. More research is needed to develop sensitive and specific diagnostic tests and to better establish the link between the virus and the development of cancer.

- **Liver cancer**—The World Health Organization estimates that globally there are about 527,000 new cases of liver cancer per year; 82 percent of which are attributable to infection with the hepatitis B and C viruses. More research is needed to determine the host factors and mechanisms involved.

In addition to cancer, there is growing evidence that other chronic illnesses may have infectious origins or “co-triggers.” Research suggests that some forms of arthritis, infertility, coronary artery disease, asthma, hypertensive renal disease, and juvenile-onset diabetes are associated with infections. The autoimmune intestinal disorders—Crohn’s disease and ulcerative colitis—are very likely to be triggered initially by a microbial factor. Consequently, the full costs of infectious diseases may be far greater than previously estimated. Confirming the infectious origins of such diseases would greatly reduce health care costs by treatment with antibiotics and other drugs and perhaps by prevention through immunization.
Biomedical research is cost effective

Focused and persistent biomedical research efforts have paid off in the past.

• Before the development and introduction of a vaccine, Haemophilus influenzae type b (Hib) was the leading cause of pediatric bacterial meningitis in the United States with more than 16,000 cases reported each year, of which 10 percent were fatal. Since the introduction of the Hib vaccine in 1989, Hib infection has decreased by 95 percent among children under age 5, resulting in savings estimated at more than $400 million per year.

• The NIAID led a 15-year research effort on safer pertussis vaccines to protect infants, leading to the successful conclusion of clinical trials showing that three new acellular pertussis vaccines are more effective and demonstrate fewer adverse events than the whole-cell vaccine. Worldwide, pertussis is responsible for an estimated 350,000 deaths annually.

• Protease inhibitors used in combination with other drugs such as AZT were shown to block the protease enzyme of HIV, thereby preventing HIV from replicating itself. In the past year, we have learned that many people with AIDS can experience dramatic improvement after treatment with these drugs.

• Chlamydial infection is the most common bacterial sexually transmitted disease in the United States, with about 4 million new cases each year at an annual cost exceeding $2 billion. If undetected and untreated the infection can lead to long-term complications such as infertility and tubal pregnancy. A highly sensitive and noninvasive urine assay that allows earlier detection of this infection even before it becomes symptomatic has been developed.

• NIAID intramural investigators developed, patented and licensed a strain of hepatitis A virus (HAV) for use in the first commercially available vaccine against HAV. Worldwide, there are more than 1.4 million cases of hepatitis A each year. While most cases occur in countries with poor sanitation, also at risk are the 30–50 million visitors to developing countries where hepatitis A is endemic. In the United States, hepatitis A accounts for more than half of reported hepatitis cases and costs more than $200 million annually in medical costs and lost wages.

• In developing countries, rotaviruses, the most common cause of severe diarrhea, affect more than 18 million infants and children under age 5 and cause an estimated 800,000 deaths annually. In the United States each year rotaviruses cause more than 3.5 million episodes of illness, 110,000 hospitalizations, and over 100 pediatric deaths. Rotavirus infections cost close to $1 billion a year in the United States. A new vaccine has been shown to be 80 percent effective in protecting against rotaviral disease and 100 percent effective in preventing dehydrating illness.
References


National Institute of Allergy and Infectious Diseases, The NIAID Research Agenda for Emerging Infectious Diseases, July 1996.


Within minutes of birth and continuing throughout every minute of every day for the rest of our lives, our bodies are exposed to a myriad of microorganisms. If we look through a microscope at the imprint of our unwashed thumb or at a swab from the inside of our mouth, we will be astonished at the large numbers and varieties of microorganisms we see. Fortunately, few of these microbes have the capacity to cause infectious diseases. In fact, we need many of these microorganisms to live a normal, healthy life. Although we are awash in “germs,” for the most part we remain free from infectious disease.

However, microbes with the potential to trigger disease occasionally invade our bodies through the air we breathe, the food we eat, the water we drink, contact with each other and with animals, or even the bite of an insect.

Under normal circumstances, our body’s natural defense barriers—skin, tears, even the tiny hairs in our nose—keep out harmful microbes. When infectious agents manage to breach our normal defense barriers, our immune system fights them off by producing antibodies and other immune elements. But when our immune systems are weakened, when our normal defense barriers are not intact, or when we come in contact with a highly invasive infectious agent that is either new to our bodies or present in large numbers, the balance shifts in favor of the microbes.

Humans have helped (often unknowingly) to tip the scales in favor of the microorganisms. Crowded living conditions, international travel, changes in food processing and handling, and misuse and overuse of antibiotics all act to improve the efficiency by which microbes spread from person to person and place to place. Counterintuitive as it may seem, technology and other aspects of human “progress” subtly change the nature of our interactions with the microbes that surround us. The result has been a burgeoning incidence of emerging infectious diseases and the resurgence of those we thought we had under control. Fortunately, basic research into the modes of transmission, diagnosis, and effective treatment of many of these emerging infectious diseases has led to successful intervention and control. However, our struggle against infectious diseases is far from over, and in some cases, we are actually losing ground.