

The Perpetual Challenge of Infectious Diseases

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AMONG THE MANY CHALLENGES TO HEALTH, INFECTIOUS DISEASES STAND out for their ability to have a profound impact on the human species. Great pandemics and local epidemics alike have influenced the course of wars, determined the fates of nations and empires, and affected the progress of civilization, making infections compelling actors in the drama of human history.¹⁻¹¹ For 200 years, the *Journal* has captured the backdrop to this human drama in thousands of articles about infectious diseases and about biomedical research and public health efforts to understand, treat, control, and prevent them.

THE UNIQUENESS OF INFECTIOUS DISEASES

Infections have distinct characteristics that, when considered together, set them apart from other diseases (Table 1). Paramount among these characteristics is their unpredictability and their potential for explosive global effect, as exemplified by the bubonic–pneumonic plague pandemic in the 14th century,^{1,12} the 1918 influenza pandemic,^{13,14} and the current pandemic of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS),¹⁵ among others. Infectious diseases are usually acute and unambiguous in their nature. The onset of an infectious illness, unlike the onset of many other types of disease, in an otherwise healthy host can be abrupt and unmistakable. Moreover, in the absence of therapy, acute infectious diseases often pose an all-or-nothing situation, with the host either quickly dying or recovering spontaneously, and usually relatively promptly, often with lifelong immunity to the specific infecting pathogen.

Not only are some infectious diseases transmissible to others, a unique characteristic among human diseases, but their transmission mechanisms are relatively few (including inoculation and airborne and waterborne transmission), well understood, and comparatively easy to study, both experimentally and in the field. In addition, such transmission is generally amenable to medical and public health interventions. Unlike many chronic and lifestyle-associated diseases resulting from multiple, interacting risk cofactors, most infectious diseases are caused by a single agent, the identification of which typically points the way not only to general disease-control measures (e.g., sanitation, chemical disinfection, hand washing, or vector control) but also to specific medical measures (e.g., vaccination or antimicrobial treatment).

Given their nature, infectious diseases are potentially preventable with personal protection, general public health measures, or immunologic approaches such as vaccination. As preventive measures have become more effective and efficient, history has shown that certain infectious diseases, particularly those with a broad global health impact and for which there is no nonhuman host or major reservoir, can be eliminated. Such diseases include poliomyelitis, which has been eliminated in the Western Hemisphere,¹⁶ and smallpox, which has been eliminated globally.⁹

Another unique aspect is that the extraordinary adaptability of infectious pathogens (i.e., their replicative and mutational capacities) provides them with a temporary evolutionary advantage against pressures aimed at their destruction. These pres-

asures include environmental factors and antimicrobial drugs, as well as the human immune response. At the same time, such adaptations provide us with opportunities to respond with new vaccine antigens, such as annually updated influenza vaccines,¹⁷ or new or different anti-infective agents. This back-and-forth struggle between human ingenuity and microbial adaptation reflects a perpetual challenge.^{12,18,19}

Infectious diseases are closely dependent on the nature and complexity of human behavior, since they directly reflect who we are, what we do, and how we live and interact with other people, animals, and the environment.¹⁹⁻³⁰ Infectious diseases are acquired specifically and directly as a result of our behaviors and lifestyles, from social gatherings, to travel and transportation, to sexual activity, to occupational exposures, to sports and recreational activities, to what we eat and drink, to our pets, to the environment — even to the way we care for the ill in hospitals and other health care environments. Moreover, microbial colonizing infections that lead to long-term carriage without disease (e.g., within the endogenous human microbiome) may influence the development of infections with exogenous microbes^{31,32} and also have an effect on general immunologic and physiologic homeostasis,^{33,34} including effects on nutritional status. Human microbiomes seem to reflect, and may even have helped to drive, human evolution.³⁵

In this struggle, infectious diseases are intimately and uniquely related to us through our immune systems. The human immune system, including the primitive innate system and the specific adaptive system,³⁶ has evolved over millions of years from both invertebrate and vertebrate organisms, developing sophisticated defense mechanisms to protect the host from microbes.³⁷ In effect, the human immune system evolved as a response to the challenge of invading pathogens. Thus, it is not by accident that the fields of microbiology and immunology arose and developed in close association long before they came to be considered distinct disciplines.

DISEASE EMERGENCE AND REEMERGENCE

Because infectious pathogens are evolutionarily dynamic, the list of diseases they cause is ever-changing and continually growing. Since newly

Table 1. Characteristics of Infectious Diseases That Set Them Apart from Other Human Diseases.

Potential for unpredictable and explosive global impact
Frequent acquisition by host of durable immunity against reinfection after recovery
Reliance of disease on a single agent without requirement for multiple cofactors
Transmissibility
Potential for becoming preventable
Potential for eradication
Evolutionary advantage over human host because of replicative and mutational capacities of pathogens that render them highly adaptable
Close dependence on the nature and complexity of human behavior
Frequent derivation from or coevolution in other animal species
Possibility of treatment for having multiplying effects on preventing infection in contacts and the community and on microbial and animal ecosystems

emerging infectious agents do not arise spontaneously, they must recently have come from somewhere else, usually from animal infections, as occurred with HIV infection, influenza, and the severe acute respiratory syndrome. This interspecies transmission underscores the importance of interdigitating the study of human and animal diseases^{19,23,38-40} and recognizing the central role that microbial reservoirs, including those in animals, vectors, and the environment, play in human infectious diseases.^{19,38} Preexisting or established infectious diseases also may reemerge in different forms, as in extensively drug-resistant tuberculosis,⁴¹ or in different locations, as in West Nile virus infection in the United States,⁴² to cause new epidemics (Table 2). Indeed, many human infectious diseases seem to have patterns of evolution, sometimes played out over thousands of years, in which they first emerge and cause epidemics or pandemics, become unstably adapted to human populations, undergo periodic resurgences, and eventually become endemic with the potential for future outbreaks (Fig. 1).^{12,19,43,44}

HISTORICAL PERSPECTIVES AND CURRENT STATUS

Just over a decade before the publication of the first issue of the *Journal*, President George Washington died of an acute infectious disease believed to have been bacterial epiglottitis.⁴⁵ Wash-

Table 2. Broad Categories of Infectious Diseases.*

Type of Disease	Description
Established infectious diseases	Endemic diseases that have been prevalent for a sufficient period of time to allow for a relatively stable and predictable level of morbidity and mortality (e.g., viral and bacterial respiratory and diarrheal diseases, drug-susceptible malaria and tuberculosis, tropical diseases such as helminthic and other parasitic diseases, nosocomial infections)
Newly emerging infectious diseases	Diseases that are recognized in the human host for the first time (e.g., HIV/AIDS, Nipah virus, severe acute respiratory syndrome)
Reemerging infectious diseases	Diseases that historically have infected humans but continue to reappear either in new locations (e.g., West Nile virus in the United States) or in resistant forms (e.g., influenza, methicillin-resistant <i>Staphylococcus aureus</i> , drug-resistant malaria) or reappear after apparent control or elimination (e.g., polio in parts of Africa, cholera in Haiti, dengue in Florida) or under unusual circumstances (e.g., deliberately released agents, including the anthrax release in 2001)

* Categories of infectious diseases include those that are newly emerging, those that have become established and may periodically reemerge, and those that have become stably endemic.¹⁹ Modern concepts that relate to emerging infections are more fully described in an influential 1992 report by the Institute of Medicine.²⁰

ington's life reflects the history of his era and provides both a window into infectious diseases two centuries ago and a benchmark for measuring our remarkable progress since then. Washington was born in 1732, just before the deadliest diphtheria epidemic on the North American continent. He was scarred by smallpox, survived multiple debilitating bouts of malaria, suffered wound infections and abscesses, nursed his brother on a tropical island as he died of tuberculosis, and even had an influenza pandemic named after him (the Washington influenza of 1789–1790). During his presidency, he stayed in the then-capital city of Philadelphia while most of the government fled during the nation's deadliest yellow fever epidemic.^{5,12} At the time of Washington's birth, there was no well-defined concept of infection or immunity, no vaccines, almost no specific or effective treatments for infectious diseases,^{3,46} and little idea that any treatment or public health measure could reliably control epidemic diseases.

During Washington's lifetime, infectious diseases were the defining challenges of human existence. No one alive then could have imagined the astonishing breakthroughs that lay ahead. In this regard, it is noteworthy that almost all the major advances in understanding and controlling infectious diseases have occurred in the past two centuries (Table 3 and interactive timeline). Experimental animal-transmission studies that were conducted soon after the War of 1812 were followed by the development of better microscopes, which linked fungi to skin diseases and protozoa to mucosal diseases — for example,

Alfred Donné's 1836 work with *Trichomonas vaginalis* and David Gruby's studies of *Candida albicans* in the early 1840s. The breakthroughs in the late 1800s, which taken together provided the compelling unifying principle of infectious diseases and must surely rank among the most important advances in the medical sciences, were the characterization of specific cultivatable microorganisms and proof of their association with specific diseases. This triumph was led by the work of Davaine and Koch in establishing anthrax as the first fully characterized infectious disease.^{47,48} This seminal process was facilitated by the development of defined criteria for establishing causality (Koch's postulates).

Additional breakthroughs followed quickly, including the discovery and characterization of pathogen-specific immune responses; the demonstration that when inactivated by heat or chemicals or grown under limiting conditions that changed certain biologic properties (e.g., attenuation), organisms or their products could safely stimulate protective responses in a host; and development of anti-infective serums and chemicals to destroy pathogens. Over the next 135 years, a wide array of vaccines and antibiotics and, more recently, antiviral agents have saved hundreds of millions of lives, greatly extended the human life span, and reduced untold suffering. Undeniably, these countermeasures against infectious disease rank among the greatest achievements in public health and medicine.

History reminds us that new challenges in infectious diseases will continue to emerge and re-



An interactive
timeline on
selected infectious
diseases from 1812
to the present
is available at
NEJM.org

emerge. We must be prompt in identifying them and devising new countermeasures. In this effort, we still follow the familiar pathway that was set down in the late 1800s for the identification and characterization, both clinical and epidemiologic, of the causative agent; the characterization of the human immune response to the pathogen; and the development of pathogen-specific diagnostic tests, treatment strategies, and public health prevention strategies such as vaccinations.⁴⁹

DIAGNOSIS AND CHARACTERIZATION OF PATHOGENS

In the late 1800s, the realization that identifiable microbes caused specific diseases led to pathogen-specific medical diagnosis. Although the time-honored techniques of growing bacteria in broth or solid cultures and staining and examining them under microscopes are still important today, newer technologies have transformed the field of microbial diagnosis. Among the first emerging epidemic diseases to be identified by one such method was the hantavirus pulmonary syndrome, a centuries-old disease caused by an unknown phlebovirus (Sin Nombre) that was discovered unexpectedly in 1993⁵⁰ by the application of a then-novel molecular genetic technique, polymerase chain reaction (PCR). This followed quickly on the 1992 discovery of the previously unknown agent causing an infectious chronic condition, Whipple's disease.⁵¹ Less than a year later, PCR-related subtraction techniques solved a century-old mystery of the cause of Kaposi's sarcoma, human herpesvirus 8.⁵² Now, less than two decades later, sophisticated, high-throughput, rapid sequencing of the genomes of pathogens not only dramatically hastens initial identification but also detects individual genetic variants,⁵³ facilitating identification of the genetic basis of drug resistance. Additional gene-based diagnostic tools include microchips and other technologies that detect short sequences of many different genes or their proteins, allowing simultaneous diagnosis or diagnostic elimination of multiple pathogens. New serologic techniques such as enzyme-linked immunosorbent assay can be many times more sensitive than traditional techniques in detecting and measuring antibodies to pathogens. Furthermore, monoclonal antibody techniques, which involve the use of cellular clones to produce antibodies against specific pathogen epitopes, have been adapted for the purposes of

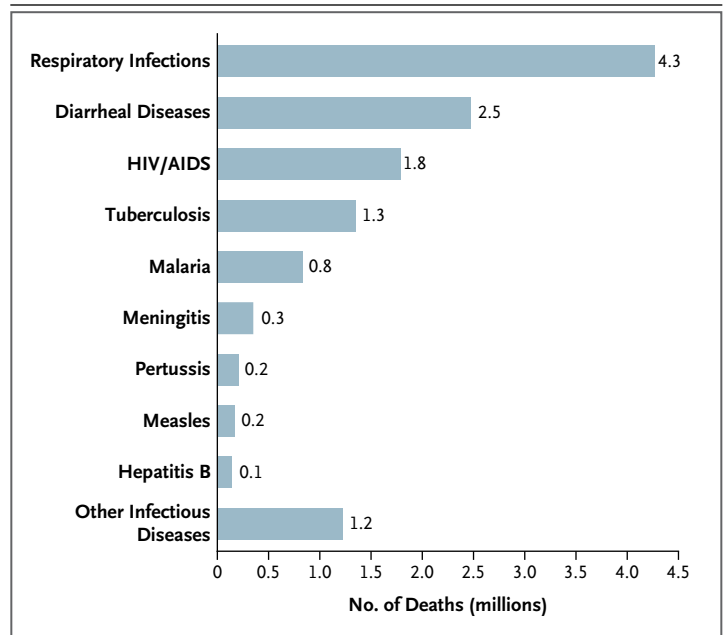


Figure 1. Leading Causes of Global Deaths from Infectious Diseases.

Of an estimated 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are believed to be caused by infectious diseases. Cause-specific mortality estimates are provided by the World Health Organization.^{43,44} The data do not include deaths from secondary infectious causes, such as rheumatic fever and rheumatic heart disease, liver cancer and cirrhosis, or other chronic diseases.

diagnosis, identification of the molecular structures of pathogens, elucidation of the natural history and pathogenesis of infectious diseases, development of conformationally accurate immunogens to be used as vaccine candidates,⁵⁴ and even treatment.⁵⁵ Many of these data-rich approaches require sophisticated bioinformatics systems (e.g., phylogenetic comparisons and genome construction analyses).

VACCINE DEVELOPMENT

Vaccines against infectious diseases such as anthrax and rabies have been produced since the late 1870s. Only in the past half century, however, have technological advances in vaccination led to dramatic changes in the field of disease prevention. The World Health Organization now estimates that each year more than 120 different types of vaccines save 2.5 million lives and with optimal uptake could save an additional 2 million.⁵⁶ Trivalent combined inactivated and live attenuated poliomyelitis vaccines were licensed in 1955 and 1962, respectively; a live attenuated trivalent vac-

Table 3. Selected Infectious Diseases of Importance from 1812 to the Present.

Disease	1812	1912	2012
Malaria	Cause unknown; wealthy persons flee to higher elevations in malaria season; "jesuit's bark" (containing quinine) used to treat symptoms	Causative organism identified in 1880 (Laveran; Nobel Prize awarded 1907); anopheles mosquito identified as principle vector (Sir Ronald Ross; Nobel Prize awarded 1902); vector-control attempts under way	Genomes of the host (human), two of the principal parasites (<i>Plasmodium falciparum</i> and <i>vivax</i>), and the principal vector (<i>Anopheles gambiae</i>) sequenced; drugs for treatment and prophylaxis; vaccines under development; successes with public health control, but malaria still causes >800,000 annual deaths
Variola (smallpox)	Cause unknown; control begins in the developed world with Jenner's 1798 publication on vaccination	Variola greatly controlled by vaccination in the developed world; developing world still has deadly epidemics	Variola eradicated in 1980 through aggressive global vaccination campaign
Plague	Cause and mode of transmission unknown; frightening disease for millennia; no good control measures; global quarantine systems not completely effective	1890s pandemic brings plague to the U.S. for the first time (1900); disease becomes enzootic and endemic, but fears of Black Death pandemic begin to subside	Plague a minor disease in U.S.; sporadic outbreaks still occur in the developing world, but fear of pandemics has subsided
Yellow fever	Cause and mode of transmission unknown; the "American Plague" is most frightening U.S. disease after deadly epidemics in 1793–1798, which led to forerunner of the U.S. Public Health Service (1798)	U.S. Public Health Service forerunner sets up Hygienic Laboratory (1887) to study the microbiology of infectious diseases, eventually becoming the National Institutes of Health; transmission by <i>Aedes aegypti</i> shown by Walter Reed team (1900); vector control efforts by Gorgas in Cuba and Panama soon lead to substantial control	Effective live attenuated vaccine developed in 1936; yellow fever is largely gone from the developed world and greatly reduced in the developing world
Tuberculosis	Cause unknown; consumption an old and feared disease; on the rise in the industrial age	Recognized as the deadliest infectious disease of the 19th century; organism discovered by Robert Koch in 1882; beginning to be controlled by public health measures and sanatorium movement	Bacille Calmette–Guérin vaccine (marginally effective against transmission of pulmonary tuberculosis) in 1921; antituberculosis chemotherapy initiated in 1950s; control in the developed world upset by HIV pandemic and in the developing world is never achieved; 1.3 million still die annually; emergence of multidrug-resistant and extremely drug-resistant tuberculosis; better vaccines actively pursued
Wound infections and puerperal fever	Causes unknown; amputations without anesthesia are often ineffective; maternal postpartum deaths common	General anesthesia introduced in 1840s; puerperal streptococcal infections controlled by hand washing in mid-19th century; aseptic technique introduced in 1867; causative organisms isolated in late 1900s	Antibiotics, first used in the late 1930s, are common by the early 1950s in the developed world
Diphtheria	"Throat distemper" (caused by diphtheria and streptococci, sometimes in combination) is a major cause of childhood deaths	Causative organism discovered in 1884; diphtheria antitoxin (1894) is the first passive immunotherapy	Vaccine produced in 1913; disease controlled in developed world
Poliomyelitis	Not well described but probably endemic	First U.S. epidemic in Vermont in 1894; recurring epidemics cause fear in the U.S. during next 60 years	Inactivated Salk and live Sabin vaccines introduced in 1955 and 1962, respectively; effective global control has led to near eradication
HIV/AIDS	Unknown	May have emerged in Africa but was not recognized	First reported in 1981; causative virus identified in 1983–1984 by Luc Montagnier and Robert Gallo; combination antiretroviral therapy greatly prolongs the lives of infected patients

cine against three unrelated diseases (measles, mumps, and rubella) was licensed in 1971; and a variety of vaccine approaches and platforms have been introduced since then. It is now possible to determine high-resolution crystallographic structures of pathogens and use this information to design vaccines directed at the most relevant epitopes in the microbe's complex structure, an approach known as structure-based vaccine design.⁵⁷

TREATMENT

Successful treatment with pathogen-immune serum was another critical breakthrough of the late 19th century.⁵⁵ This approach to therapy also encouraged scientists to develop chemicals to kill the specific pathogens that they were regularly identifying. Ehrlich succeeded first in 1910 with his magic bullet against syphilis (arsphenamine, or salvarsan⁵⁸). Within two decades, a new generation of scientists was working on what would eventually be called antibiotics. As a result of these efforts, sulfa drugs were developed in 1936, and penicillin in 1943.^{59,60} In the United States, tuberculosis had been only partially controlled by public health measures and incompletely effective vaccines.⁶¹ It was not until the introduction of specific anti-tuberculosis therapy in the 1950s⁶² that sanatoriums were emptied and cases of active disease were substantially reduced. Antibiotics have revolutionized the treatment of many other important bacterial infections and have saved many millions of lives since their introduction.

When antiviral drugs were first developed in the 1960s, they did not seem to be particularly promising, with a few exceptions. In response to the HIV/AIDS pandemic, however, the development of antiretroviral drugs markedly expanded the arsenal of available antiviral agents and invigorated the research-and-development pathway for these important drugs. Effective combinations of powerful antiretroviral drugs have led to substantial prolongation of the lives of millions of persons with previously almost invariably fatal HIV infection, a true landmark in therapies for infectious diseases.^{15,63}

All antibiotic and antiviral drugs, however, share an inherent weakness: the organisms against which they are directed almost invariably evolve mechanisms of resistance. Bacteria become resistant by a variety of mechanisms.⁶⁴ The evolution of antimicrobial resistance is enhanced by

overuse of antibiotics in animals and by inappropriate use in humans. Many viruses, particularly RNA viruses such as influenza virus, rapidly develop mutations even in a single brief replication cycle. A number of approaches have been pursued to meet the ever-present challenge of antimicrobial resistance. The development of new classes of antibiotic, antiviral, and antiparasitic agents aimed at diverse microbial targets, often with the use of high-throughput screening of compounds,⁶⁵ is strengthening and broadening the therapeutic armamentarium. In addition, combination therapies (e.g., antiretroviral agents for HIV infection and multidrug approaches to tuberculosis) have proved to be successful in slowing the emergence of resistance.

PUBLIC HEALTH ACHIEVEMENTS

Breakthroughs in the field of infectious diseases have had far-reaching effects, including the realization of the critical importance of clean water and basic sanitation and hygiene for the prevention of a great number of infectious diseases. In addition, disease-specific approaches to prevention and treatment have led in many cases to the widespread control of diseases that historically have caused substantial morbidity and mortality.⁶⁶ The treatment of infectious diseases is in itself a prevention measure, limiting or preventing transmission to others. Eradication, the ultimate goal in facing the threat of an established or emerging infectious disease, is no longer unrealistic. Specifically, in addition to the millions of lives saved by vaccines and antibiotics, certain infectious diseases have been eliminated from large regions of the world or even completely eradicated, an accomplishment rarely, if ever, seen in other medical disciplines. In 1980, smallpox became the first eradicated disease,⁹ making this among the most momentous achievements in human disease control. In May 2011, the veterinary morbillivirus disease rinderpest was declared eradicated, and its presumed descendant, human measles virus, is now being targeted for eradication.⁶⁷ Poliomyelitis has been eliminated from several regions of the world, and it is hoped that within a reasonable period, it will be eradicated globally.⁶⁸ Dracunculiasis (guinea worm disease) is also almost completely eradicated.⁶⁹ These are just a few examples of what has been and can be accomplished by aggressive and concerted public

health measures using the tools provided by basic and clinical research.

NEW VISTAS

An unanticipated outcome of the explosion of information concerning the microbial world is the recognition that a growing number of chronic diseases that were once attributed to host, environmental, or lifestyle factors or to unknown causes are actually directly or indirectly caused by infectious agents that potentially can be controlled through prevention and treatment. For example, liver cancer and cirrhosis are complications of hepatitis B and C infections, cervical cancer is a complication of human papillomavirus (HPV) infection, and gastric and duodenal ulcers may result from *Helicobacter pylori* infection.⁷⁰⁻⁷² Vaccines against two of these agents, hepatitis B and HPV, are already in use, exemplifying the concept of cancer-preventing vaccines. *H. pylori* infection can be cured with antibiotics, and chronic hepatitis B and C infections are being treated by means of antiviral regimens with growing success rates. Certain autoimmune conditions have also been attributed to infections. For example, enteric microbes have been associated with inflammatory arthritides, and *Campylobacter jejuni* and certain viruses have been associated with the Guillain-Barré syndrome.⁷³ In addition, with new technologies and approaches, scientists are exploring new facets of microbiology, including the role of the human microbiome in maintaining homeostasis in the ecosystems of our bodies and its possible relationship to conditions such as obesity and inflammatory bowel disease.⁷⁴

THE PERPETUAL CHALLENGE

We are living in a remarkable era. Almost all the major advances in understanding and controlling infectious diseases have occurred during the past two centuries, and momentous successes continue to accrue. These breakthroughs in the prevention, treatment, control, elimination, and potential eradication of infectious diseases are among the most important advances in the history of medicine. Nevertheless, because of the evolutionary capacity of infectious pathogens to adapt to new ecologic niches created by human endeavor, as well as to pressures directed at their elimination, we will always confront new or reemerging infectious threats. Our successes in meeting these threats have come not just from isolated scientific triumphs but also from broad approaches that complement the battle against infectious diseases on many different fronts, including constant surveillance of the microbial landscape, clinical and public health efforts, and efficient translation of new discoveries into disease-control applications. These efforts are driven by the necessity of expecting the unexpected and being prepared to respond when the unexpected occurs. It is a battle that has been well fought for more than two centuries but that will almost certainly still be raging, in now-unimagined forms, two centuries from now. The challenges are truly perpetual. Our response to these challenges must be perpetual as well.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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