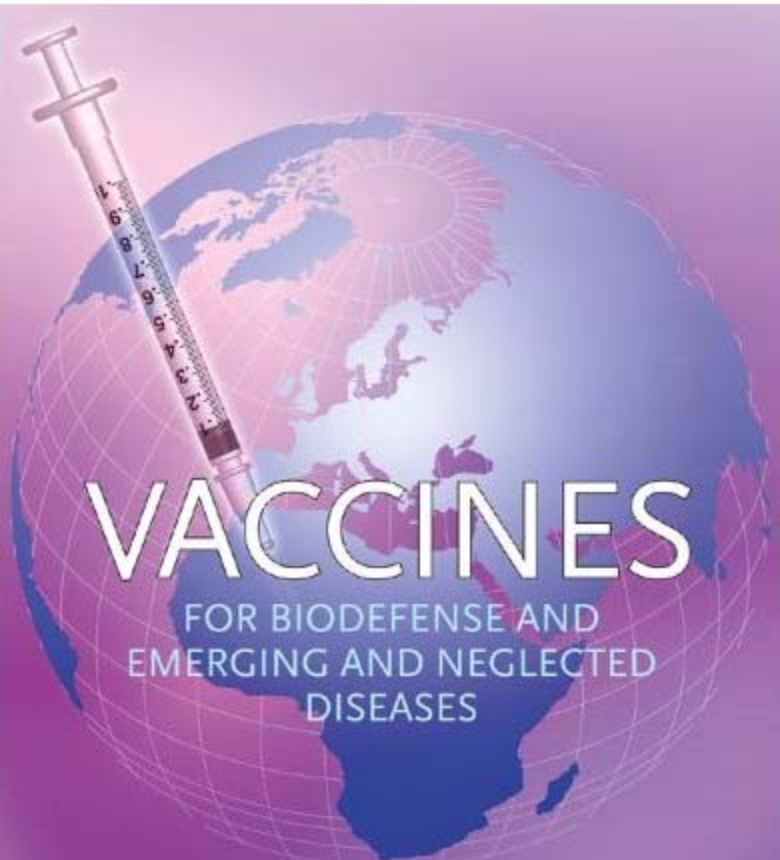

VACCINES

FOR BIODEFENSE AND EMERGING AND NEGLECTED DISEASES

EDITED BY
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Preface

"Quiet the little feet that trod
So merrily the floor
The little hands that clasped my neck
Will clasp my neck no more.
Ah! Children mine and yet not mine
For a few years were given
And then recalled to draw my heart,
Nearer to God and Heaven."

Henry Whinery, who drove the stage coach between San Jose and Santa Cruz, California saw two of his children Harry F. Whinery, (age 5 yrs, 9 mo) and Martha Whinery (age 7 yrs, 5 mo) die of Diphtheria on December 6, 1876.

Vaccines have had a greater impact on human health than any other biomedical development. Over the past three centuries vaccines have facilitated the eradication of one infectious disease, smallpox, and have limited the scourge caused by more than 25 enteric, respiratory, genitourinary and zoonotic and vector-borne pathogens including measles, polio, hepatitis B, yellow fever, and *Haemophilus influenza* type B. Despite the successes there remains enormous work to be done. Infectious diseases continue to be the number one cause of death globally claiming 20 million lives yearly. Old threats such as malaria, dengue, and syphilis have yet to be tamed. Over the past 25 years there has been a dramatic increase in newly recognized or emerging pathogens including human immunodeficiency virus, hepatitis C virus and *Helicobacter pylori*; however the development of successful vaccines has not kept pace with the discovery of these new perils. Increases in international travel and migration have made re-emerging diseases such as tuberculosis and influenza global menaces. As the world strives to achieve the ambitious Millennium Development Goals, resource poor countries struggle to overcome the burden caused by neglected diseases like trypanosomiasis and hookworm. In addition, the risk of microbes as biothreat agents, such as smallpox, anthrax and plague, continues to present a danger to mankind in the 21st century.

This comprehensive new textbook authored by leading authorities is intended to inform researchers, clinicians, public health specialists and policy makers regarding the current state of development of vaccines for emerging and neglected diseases and biothreat agents. Detailed information regarding epidemiology, clinical disease, management, immunology, pathogenesis, as well as vaccinology is presented for each pathogen. The book also provides in-depth information regarding the processes that are critical to the generation of these vaccines to the marketplace. This includes chapters on vaccine platforms, preclinical development, regulatory approval, clinical trials, manufacture and post licensure issues.

The editors would like to thank our many colleagues whose outstanding contributions made this book a reality. We would also like express our appreciation to Lisa Tickner and Carrie Bolger of Elsevier for their able and professional assistance.

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Lawrence R. Stanberry, M.D., Ph.D.

Foreword

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Vaccination is the medical practice that together with clean water had the greatest impact on human health during the 20th century. Thanks to vaccines, devastating diseases that had been responsible for much of the morbidity and mortality recorded were eliminated. These include smallpox, poliomyelitis, tetanus, diphtheria, pertussis, hepatitis B, *Haemophilus influenzae*, measles, mumps, and rubella, which killed or disabled millions of people. Meningococcal meningitis, perhaps the last disease that can attack in a few hours and kill healthy children and young people, is also on its way to being conquered by vaccination. Now that all these diseases have been controlled, is there a role for vaccination in the 21st century?

Clearly the 70 chapters of this book show that we still have a long way to go before we can conquer all the diseases that can be addressed by vaccination. There is increased interest in emerging and neglected diseases, which have not been a priority for vaccine developers, thanks to the technological revolution of the last decades that increased the feasibility of developing new vaccines and the renewed business interest on vaccines that emerged during the last 5 years.

Let us look at the increased feasibility of vaccines first. A recent review of the history of vaccination concluded that the probability of success in vaccine development is highest when protection is mediated by antibodies and antigens that have no or limited antigenic variability (Rappuoli, 2007). In a graph representing the type of immunity and the antigenic variability on the vertical and horizontal axes, vaccines that have the highest probability of success are in the upper right quadrant and the risk in vaccine development increases moving toward the intersection of the two (Fig. 1). Accordingly, vaccines for which T-cell immunity is critical for protection or protective antigens are highly variable have an increased degree of failure during development. In Fig. 1 I have tried to rank the vaccines discussed in this book based on the above-mentioned criteria. From the figure it is clear that the majority of the vaccines reside in the upper right quadrant, which belongs to the pathogens that can be addressed by antigens that meet the validated criteria for vaccine success, that is, they induce an antibody-mediated protection and they are not

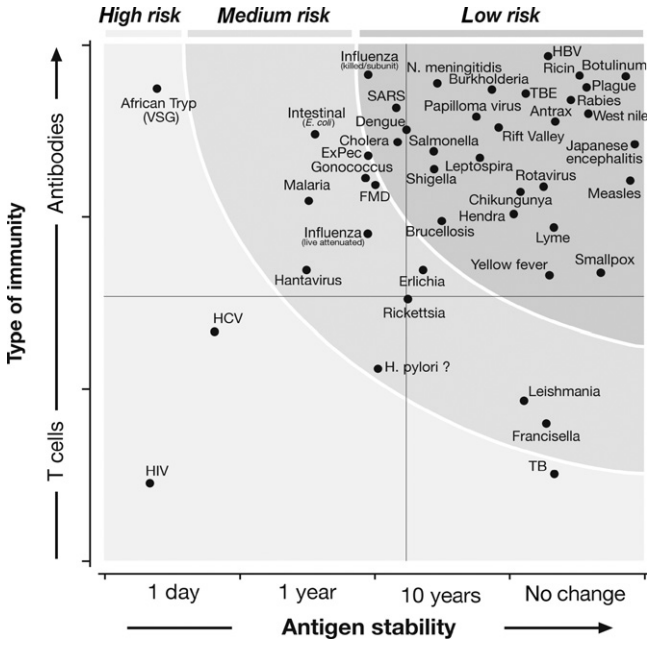

FIGURE 1 Graph representing the type of immunity and the antigenic variability.

highly variable. Therefore, in most cases, vaccines for neglected and emerging diseases can be developed using well-established technologies.

Thanks to technologies such as recombinant DNA, conjugation, genomics, and the increased understanding of the immune system, the feasibility of vaccine development has increased a great deal. Good examples are the several recombinant and conjugate vaccines already licensed, and several vaccines developed using genomics (reverse vaccinology) that are in development. Reverse vaccinology is perhaps the most powerful tool for vaccine development that has become available lately. In fact, the availability of genomic sequences allowed us to use computers to search the entire genetic repertoire for protective antigens, thus increasing by several orders of magnitude the numbers of antigens available for vaccine development. With many more antigens available for each pathogen, it is now possible to select those antigens that respond to validated principles, such as limited or absent antigenic variability and antibody-mediated protection.

An important minority of the vaccines described in this book resides in the middle or left quadrant of Fig. 1. These are the vaccines that are not yet within the reach of today's technologies and developing these vaccines requires bridging science gaps such as learning to develop vaccines based on T-cell-mediated protection. Today these vaccines are mostly addressed by using innovative immunostimulatory molecules and adjuvants, replicating or nonreplicating viral vectors, prime-boost regimens, and so forth. An alternative approach can be to bring them to the comfort zone of upper right quadrant by learning how to engineer immunosilent conserved epitopes to become immunodominant. A good example of this is HIV wherein we know that antibodies such as b12 that recognize the conserved CD4 binding site would be able to protect from infection. However, we are unable to make this epitope immunodominant and therefore we cannot yet make this vaccine. We believe that a systematic approach to the structural properties of immunodominant and immunosilent epitopes can provide the scientific rationale that in the future may allow us to engineer immunodominant epitopes. A rational approach to the 3D structure of antigens (structural vaccinology) is one of the basic aspects of vaccine research that should be a priority.

In conclusion, with a few exceptions, the majority of the vaccines addressed in this book are within the reach of today's technologies; the question is therefore whether or when they will be developed. Unfortunately, technical feasibility is only one of the hurdles in vaccine development. Even more important is often whether there is a market that can justify the huge investment that is necessary to bring vaccines to licensure. Vaccines today are developed by few global vaccine manufacturers that can only afford to invest in those vaccines that have a high probability of success in the market. With few exceptions, most of the vaccines addressed in this book are "neglected" because they do not have a market that justifies their development; as a consequence, the probability that they will be developed is low. In fact, for these vaccines the basic research and initial clinical trials will be carried out in academia and small biotechs funded by the public sector. However, the gestation of vaccines, the phase during which a discovery is transformed into a potential product, is unlikely to happen. As discussed in this book, during this phase of the vaccine development, pathogens (or their genomes) are systematically screened to identify the best antigens, the antigens are prioritized using in vitro assays and animal models that are relevant to making decisions, the selected antigens are engineered and expressed in hosts suitable for industrial scale, and the composition of the vaccine is defined using adjuvants suitable for man. Then, production of the candidate vaccine is adapted to industrial needs; it is scaled up and produced in cell lines suitable for GMP manufacturing. A robust formulation is developed; the vaccine is produced under GMP conditions and tested for stability. Toxicology studies are performed, regulatory documents are submitted to regulatory agencies, and the vaccine is finally tested for safety and for proof of concept in man. Unfortunately, the results of this phase, which is perhaps the most critical for vaccine development, are not suitable for publication in good journals and therefore there is no incentive for people in academia to embark in this area. In addition, the knowledge to do the work required in this phase lacks in academia; it is not even present in most biotechs and vaccine manufacturers in developing countries. However, five or six large vaccine manufacturers have the traditional knowledge and the necessary investment to carry out this obscure but essential part of the work. In fact many of the failures in vaccine development are due to the poor understanding and underestimation of this phase. In order to fill this gap in vaccine development, recently a new institute has been established. This is the Novartis Vaccines Institute for Global Health (NVGH), an institute with a nonprofit mission dedicated to the development of effective and affordable vaccines for neglected infectious diseases in developing countries. By having access to all the know-how and technologies available with a large vaccine manufacturer, and having neglected diseases as a mission, this institute has prospects of being successful in this area.

Despite difficulties in filling technical and structural gaps the field has never been as promising as today. Thanks to the vast progress in technology

and the renewed recognition of the enormous value that vaccines bring to the society, the field of vaccine development is moving beyond its 20th century renaissance. Vaccines today are usually given to prevent diseases that parents and pediatricians have never seen; in their minds vaccines are no longer immediate lifesavers but tools that improve the quality and duration of life. In agreement with this new vision, thanks to the scientific progress, new vaccines target infections such as HBV and HPV that can result in cancer decades after infection; they hold great promise for preventing devastating outbreaks such as pandemic influenza and are being explored for the control of chronic, metabolic, and neurological diseases. Vaccines targeting hypertension, drug addictions, and cigarette smoking are examples of cases that are not traditionally tackled by vaccination. Although some difficult targets such as HIV presently remain beyond the reach of technical feasibility, a new vision is emerging that views vaccines as friendly and safe tools for a global health for all ages and all populations around the world. In this vision, one of the most important missions is to be ready and promptly tackle those diseases that are traditional targets for vaccination, that is diseases caused by emerging infectious agents, traditional infectious agents causing diseases in developing countries that cannot afford the cost of vaccine development, and those infectious agents that have the potential to be improperly used as biological weapons. Although investing in the development of these vaccines is going to be a cost to our society, this can be one of the best investments for improving the quality of life of people globally and for minimizing the risk of biological agents as weapons of terror.

The developmental risk of the vaccines discussed in this book is based on the predicted type of immunity and antigen stability. The graph is adapted from Rappuoli (2007).

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SECTION I

BIOTHREATS AND EMERGING INFECTIOUS DISEASES

CHAPTER

1

Agents of Emerging Infectious Diseases

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OUTLINE

ABSTRACT

Dramatic improvements in the control of infectious diseases in developed countries owing to socioeconomic changes, vaccines, and antibiotics during the first seven decades of the 20th century led to the mistakened concept that infectious diseases would no longer be a concern. Since the declaration of victory in the war against infectious diseases in 1967, approximately 50 new disease agents have been identified. Nearly every type of etiologic agent and clinical manifestation have been involved including acute respiratory infections (e.g., H5N1 influenza A, SARS, hantaviral cardiopulmonary syndrome, and Legionnaires' disease), central nervous system involvement (e.g., West Nile encephalitis, Nipah virus encephalitis, and prion diseases), enteric infections (e.g., *Helicobacter pylori* gastric and duodenal diseases, cryptosporidiosis, microsporidioses, and Shiga toxin diseases), systemic bacterial diseases (e.g., Lyme disease, six new rickettsioses, three new human ehrlichioses, bartonelloses, and staphylococcal and streptococcal toxic shock syndrome), viral hemorrhagic fevers (e.g., Marburg, Ebola, Lassa, Bolivian, Argentine, and Venezuelan hemorrhagic fevers), human retroviral infections (e.g., HIV1 and 2 and HTLV-I and II), new human herpesviruses (HHV6, HHV7, and HHV8), and the viral agents of hepatitis A, B, C, D, and E.

There are the reciprocal threats that a bioterror agent (e.g., smallpox virus) could cause a newly emerging infectious disease (EID) and that an agent of emerging infections (e.g., SARS-coronavirus or Rift Valley fever virus) could be disseminated by terrorists.

Vaccines offer a critically important potential countermeasure against the effects of these and future EIDs. An aggressive approach to developing prototype vaccines against each new class of etiologic agent must be driven by public health initiatives because commercial interests will not undertake these projects. The microbe must be completely characterized biologically, molecularly, and genetically. An accurate animal model of the human infectious disease should be developed. The mechanisms of vaccine-induced protective immunity must be elucidated and the antigens that stimulate these mechanisms of protective immune memory identified. Preclinical testing of vaccine candidates should then be completed in the animal models.

It would be most effective if subunit vaccine platforms were developed in which new antigen cassettes could be inserted and FDA approval obtained using one or more prototypes. Experience in manufacturing and a track record of effectiveness and safety for vaccines against numerous emerging infectious agents could be achieved for veterinary diseases caused by organisms that also cause emerging human infections (e.g., West Nile virus and ehrlichioses).

In the United States, these approaches are driven currently by individual investigator initiative in pursuing the scientific questions through grants from the National Institute of Allergy and Infectious Diseases. Progress occurs, but not at the desired level. An emerging infection with high transmissibility (e.g., $R_o = 10$) and a case-fatality rate of 15% would cause global devastating effects at a level on the order of magnitude of a nuclear war. Our efforts to prepare for EIDs fall far short of nuclear attack preparedness during the Cold War.

INTRODUCTION

A rather optimistic statement in 1967 from the US Surgeon General proclaimed stated that "the war against infectious diseases has been won." The emergence and re-emergence of infectious diseases during the past four decades has been astounding and has obviously proved this highly publicized statement wrong. A former director of the National Institute of Allergy and Infectious Diseases stated in 1981 that microbial diversity and evolutionary vigor were still dynamic forces threatening mankind. With the advent of revolutionary research tools, our view of the world of microbial diversity continues to expand

astronomically. As an example, a random sample of seawater near Bermuda yielded DNA sequences never known before. The most accepted definition of an emerging and re-emerging infectious disease is "a disease that has newly appeared in the population or has existed previously, but is rapidly increasing in incidence and geographic range." Another widely cited definition is a "new emerging or drug resistant infection whose incidence in humans has increased within the last two decades, or whose incidence threatens to increase in the near future." Strictly speaking all infectious diseases have "emerged" at one time or another. Thus, the definitions are rather arbitrary. The emergence of *Mycobacterium tuberculosis* and *Plasmodium falciparum* as human pathogens probably occurred within the last few tens of thousands of years. Other pathogens required rather large human populations interacting closely so that human–human transmission would occur such as with measles and smallpox viruses. HIV probably made the jump to humans 60–75 years ago. Emerging infections are further classified by others as newly emerging, re-emerging/resurging, and deliberately emerging. The factors involved in the process of emergence and re-emergence are extremely complex and have to do with the microbes themselves, the environment, and the hosts, a triad well known to any scientist who works in the field of infectious agents. The Convergence Model tries to explain all factors that affect the host–microbe interaction. This interaction is affected by interlocking domains, namely genetic and biologic factors, ecologic factors, physical environmental factors, and social, political and economic factors.

EMERGING INFECTIOUS DISEASES SINCE 1967

We have attempted to create a comprehensive list of infectious diseases that fall into this category (Table 1.1). A discussion of the clinico-epidemiological characteristics of the most representative emerging infectious diseases (EIDs) follows. We have classified EIDs based on clinical presentation (syndromes such as pneumonia, encephalitis, systemic bacterial infection, enteric infection, and viral hemorrhagic fever).

EMERGING INFECTIONS CAUSING ACUTE RESPIRATORY INFECTIONS

Acute respiratory infections are the leading cause of mortality from infectious diseases around the world. In 2003, 37 million deaths were due to acute lower respiratory tract infections. Upper respiratory tract infections, although important from the point of view of morbidity, are rarely fatal. In developed countries the main culprits are influenza and bacterial pneumonias. In underdeveloped countries, the highest mortality rates are seen in children less than 5 years of age with viral pneumonia caused by respiratory syncytial virus, parainfluenza viruses, influenza viruses, and adenoviruses. Bacterial respiratory agents include *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Staphylococcus aureus*.

VIRAL PULMONARY SYNDROMES

Influenza Viruses

These viruses belong to the family Orthomyxoviridae and are enveloped, negative sense, single-stranded, segmented, RNA viruses responsible for recurrent epidemics of febrile respiratory disease every 1–2 years. Influenza viruses are further classified as A, B, and C based on antigenic characteristics. Influenza B and C viruses only undergo antigenic drift as compared with influenza A viruses that can undergo antigenic shift in addition to antigenic drift. Antigenic shifts are responsible for the major pandemics seen with influenza A viruses, three of which occurred in the 20th century, including the highly lethal 1918/1919 pandemic that killed tens of millions of people around the world. Pandemics do not occur with influenza B and C viruses. In fact influenza C causes a mild disease without seasonality, and influenza B causes severe disease confined to the elderly and other persons at high risk. Influenza A viruses are divided into subtypes based on the presence of different hemagglutinin (H) and neuraminidase (N) molecules on their surface. Sixteen distinct hemagglutinins and nine different neuraminidases have been described to date. Influenza viruses are among the most contagious human viruses with attack rates of 10–40% during epidemics. Epidemics are seasonal (winter) in temperate regions and can occur year round in tropical areas. Since the last influenza pandemic in 1968, the predominant virus circulating around the world is the H3N2 subtype that undergoes minor mutations in the H and N proteins and is responsible for yearly outbreaks. In 1977, the H1N1 virus (the same subtype that was responsible for the 1918 pandemic) was reintroduced and is currently co-circulating with H3N2 virus. However, isolated cases of human influenza due to avian viruses such as H5N1 are cause for concern among health professionals around the world because of the high lethality and the possibility that development of efficient

TABLE 1.1 Infectious diseases with agents identified since "The end of the war against infectious diseases" 1967–2004

Year	Agent	Disease
1967	Marburg virus	Marburg hemorrhagic fever
1969	Lassa virus	Lassa fever
1971	JC virus	Progressive multifocal leukoencephalopathy
1972	Norovirus	Norwalk diarrheal illness
1973	Rotavirus	Major cause of infantile diarrhea worldwide
1975	Parvovirus B19	Fifth disease; aplastic crisis in chronic hemolytic anemia; hydrops fetalis; chronic anemia of immunosuppressed patient
1976	*Vibrio vulnificus*	Sepsis and necrotizing fasciitis
1976	*Cryptosporidium parvum*	Human cryptosporidiosis
1977	Ebola virus	Ebola hemorrhagic fever
1977	*Clostridium difficile*	Pseudomembranous colitis
1977	*Legionella pneumophila*	Legionnaires' disease, Pontiac fever
1977	Hantaan virus	Hemorrhagic fever with renal syndrome
1977	Delta viral hepatitis	Hepatitis B virus-associated hepatitis
1977	*Campylobacter* sp.	Enteric pathogens distributed globally
1979	*Cyclospora cayetanensis*	Diarrheal illness
1980	HTLV-I	T-cell lymphoma-leukemia; tropical spastic paresis
1981	*Staphylococcus aureus* toxin	Toxic shock syndrome
1982	*Borrelia burgdorferi*	Lyme disease
1982	*Escherichia coli* 0157:H7	Hemorrhagic diarrhea, hemolytic uremic syndrome
1982	HTLV-II	Associated with neurologic syndromes
1983	HIV-1	AIDS
1983	*Helicobacter pylori*	Gastric and duodenal ulcers
1984	*Hemophilus influenzae aegyptius*	Brazilian purpuric fever
1985	*Enterocytozoon bieneusi*	Microsporidiosis
1986	*Chlamydia pneumoniae*	A major cause of pneumonia
1988	Human herpesvirus 6	Exanthem subitum (roseola infantum)
1989	*Rickettsia japonica*	Japanese spotted fever
1989	Hepatitis C virus	Parenterally transmitted nonA–nonB hepatitis
1990	Hepatitis E virus	Enteric nonA, nonB hepatitis
1990	*Balamuthia mandrillaris*	Leptomyxid amebic meningoencephalitis
1990	Human herpesvirus 7	Another cause of exanthem subitum
1991	Guanarito virus	Venezuelan arenaviral hemorrhagic fever
1991	*Encephalitozoon hellem*	Microsporidiosis
1991	*Ehrlichia chaffeensis*	Human monocytotropic ehrlichiosis
1992	Barmah Forest virus	Febrile polyarthralgia
1992	*Vibrio cholerae* 0139	New strain associated with epidemic cholera
1992	*Bartonella henselae*	Cat scratch disease; bacillary angiomatosis; endocarditis
1992	*Rickettsia honei*	Flinders Island spotted fever
1992	*Tropheryma whippelii*	Whipple's disease
1993	Sin Nombre hantavirus	Hantavirus cardiopulmonary syndrome
1994	*Anaplasma phagocytophilum*	Human granulocytic anaplasmosis
1994	Hendra virus	Acute respiratory syndrome, meningitis
1996	Human herpesvirus 8	Kaposi's sarcoma, Castleman's disease, primary effusion based B-cell lyphoma

(*Continued*)

TABLE 1.1 (Continued)

Year	Agent	Disease
1997	*Rickettsia slovaca*	Tick-borne lymphadenopathy
1999	*Ehrlichia ewingii*	Ehrlichiosis ewingii
1999	Nipah virus	Encephalitis
2001	Human metapneumovirus	Upper and lower respiratory infections
2003	SARS-CoV	Severe acute respiratory syndrome (SARS)
2004	Monkeypox virus	Human monkeypox (USA outbreak)

person-to-person transmission could trigger another pandemic. The first case of human influenza due to H5N1 was described in 1997, and the infection re-emerged in Southeast Asia in 2004. Death rates in domestic birds in Southeast Asia are staggering. Other avian influenza viruses have also emerged in other parts of the world such as H7N7 in the Netherlands causing an outbreak of hemorrhagic conjunctivitis in humans. Influenza A viruses are capable of infecting a wide variety of animals including birds, horses, marine mammals, swine, and humans. The most important reservoir is wild aquatic birds (water fowl, ducks, and shorebirds). These animals can carry different subtypes in their gut, and some viruses are capable of infecting domestic poultry. The ability of avian influenza viruses to infect humans is rather restricted as is the ability for transmission from person-to-person. Because of their segmented genomes, influenza A viruses have the potential to swap or reassort genes when present in the same host or "mixing vessel" such as pigs (these animals have cell surface receptors that allow cellular entry of both bird and human influenza viruses). If the favorable environmental conditions are present, human influenza viruses can coexist with avian viruses in pigs, and new reassortants may be produced with potentially enhanced ability to infect humans.

Clinically, the human disease manifests as a severe febrile illness with abrupt onset, myalgias, severe malaise, dry cough, arthralgias and nasal discharge. Most patients recover from the acute phase of the disease in 3–5 days. Complications include primary influenza viral pneumonitis, which was first well documented in the 1957–1958 pandemic. However, it is widely accepted that this and bacterial superinfections were the causes of death of millions of persons in the 1918 pandemic. These patients progress to acute respiratory failure rapidly, and the main pathologic finding is that of diffuse alveolar damage with a hemorrhagic component. Other complications include secondary bacterial pneumonias.

Severe Acute Respiratory Syndrome (SARS)

An explosive outbreak of severe adult respiratory distress syndrome (ARDS) occurred in residents of Hong Kong and persons who had visited Hong Kong early in 2003. A cluster of cases that had started in November 2002 also occurred in the Guangdong Province of China. After a few months of excellent "detective" work by health agencies and research laboratories worldwide, a new coronavirus was identified as the culprit. Between November 2002 and July 2003, 8096 cases were reported from nearly 30 countries, but the vast majority of cases occurred in mainland China and Hong Kong. The case-fatality rate was between 7 and 17% and approached 50% in the elderly. High mortality rates were also observed in patients with preexisting conditions such as diabetes and cardiopulmonary diseases.

An animal reservoir for SARS-CoV appears likely to be bats, but the virus also has been isolated from civet cats and other wild animals in markets in China where cross-species infections may have occurred. Other coronaviruses in humans have cyclical patterns of circulation. It is suspected that SARS-CoV could reappear in humans. In severe cases, the main finding is diffuse alveolar damage leading to acute respiratory insufficiency. In milder cases, fever, malaise and mylagia are the main manifestations.

Human Metapneumovirus

This viral pathogen was first identified in 2001 in an outbreak of upper and lower respiratory illness in the Netherlands. The agent is a paramyxovirus, subfamily Pneumovirinae in which two genera have been established: Pneumovirus (respiratory syncytial virus, RSV) and Metapneumovirus. The disease spectrum is not completely known but can manifest as severe upper and lower respiratory infections in children and adults especially in patients with previous cardiopulmonary conditions. The disease is similar to RSV

infection and can account for up to 10% of acute upper respiratory tract infections in which another etiologic agent has not been identified. Asthmatic exacerbations have also been related to metapneumovirus infections. Retrospective serological studies have established that this virus has been circulating in humans for at least 50 years.

Hantavirus Cardiopulmonary Syndrome (HCPS)

Sin Nombre virus (SNV) was the first hantavirus in the Americas associated with HCPS. The disease was first described in an outbreak in the Four Corners area of the southwestern US in 1993. SNV belongs to the genus Hantavirus within the family Bunyaviridae. The vast majority of viruses within this family are arthropod-borne zoonoses, with the exception of hantaviruses, which are not vector-borne. Hantaviruses are found in wild rodents, which excrete the virus in urine and saliva for months. SNV is the most important pathogenic hantavirus in North America and causes chronic infections in deer mice (*Peromyscus maniculatus*). In North America, other viruses within the same genus associated with HCPS have been described such as New York virus found in the white footed deer mouse (*Peromyscus leucopus*). In South America, the main representative of the genus is Andes virus, which is responsible for HCPS in Chile and Argentina, and is the only hantavirus for which human-to-human transmission has been documented. In 1978, another hantavirus associated with hemorrhagic fever and renal syndrome (HFRS) in the Korean peninsula was isolated. This infection is endemic across the Asian continent.

The main mode of transmission is through aerosol spread of infected excreta (urine and possibly feces) and less frequently by bites of infected rodents. HCPS is an explosive febrile illness accompanied by myalgias and sometimes abdominal pain. In 4–5 days, respiratory symptoms appear and rapidly progress to severe noncardiogenic pulmonary edema with subsequent hypoxia and shock within hours. Cardiac dysfunction also occurs.

BACTERIAL PULMONARY SYNDROMES

Legionnaires' Disease

An outbreak of pneumonia in 1976 in Philadelphia, Pennsylvania during the state American Legion convention affected 221 people, 34 of whom died from the infection. In 1977, Dr. McDade and Dr. Shepard at the CDC isolated the etiologic agent, a fastidious gram negative organism later named *Legionella pneumophila*. This bacterium has been responsible for subsequent epidemics and sporadic cases, and retrospective studies determined that it had been responsible for outbreaks of pneumonia in the 1950s and 1960s. *Legionella* species are naturally occurring aquatic bacteria that grow in warm water, especially in cooling towers, water heaters and plumbing, hence the propensity to cause nosocomial and community outbreaks (hotels and other facilities). Free-living amebas also support the intracellular growth of *Legionella spp.* More than 20 *Legionella* species have been described affecting humans, thus the general name of legionellosis.

The disease occurs both sporadically (65–75% of cases) and in outbreaks or epidemics. Recent epidemics have occurred in Spain (2001, 700 cases), England (2002, 130 cases), and the Netherlands (1999, 188 cases).

Transmission is by aerosolization of contaminated water sources. Once in the alveoli of the lung, the bacteria are phagocytosed by alveolar macrophages through coiling phagocytosis, and multiplication occurs. The bacteria are then released into the alveolar space by dying macrophages where they can invade other alveolar macrophages. A type IV secretion system is important in promoting intracellular infection including inhibition of phagolysosomal fusion. The lungs reveal patchy-to-confluent bronchopneumonia that may be complicated by pleural effusions or cavitation in a minority of cases. Extrapulmonary infection is rare.

Tuberculosis

Tuberculosis (TB) is as old as civilization itself as demonstrated by evidence of spinal tuberculosis in Egyptian mummies and Neolithic and pre-Columbian bones. However, tuberculosis did not become a major public health problem until the 17th and 18th centuries during the Industrial Revolution. Tuberculosis also ravaged (and still does) the native American populations after Columbus' voyages to the Americas. In the United States, tuberculosis saw a steady decline in the middle part of the 20th century until 1985 when the incidence climbed again principally due to the appearance of HIV. Other factors included deterioration of living conditions, intravenous drug abuse, and underfunding of tuberculosis control programs. However, since the mid-1990s rates have declined and in 2002 reached the lowest incidence in history from the time statistics became available. This control is the result of better anti-HIV therapies, intensified diagnosis, aggressive and monitored anti-TB treatment and prevention efforts. However, not all is good news in

the TB world. The appearance of multidrug resistant strains of *M. tuberculosis* is a challenge recalling the preantibiotic era. In addition, *M. tuberculosis* is the number one killer worldwide (2 million deaths and 8 million new cases diagnosed each year), and approximately 2 billion people are infected.

More than 95% of infections caused by *M. tuberculosis* are acquired by inhalation of aerosols generated from an infectious patient. The initial focus of infection (Gohn's lesion) later develops into Gohn's complex (accompanying infected draining hilar lymph node lesions), and in most cases the infection is contained by the immune system. In the most severe cases, the infection disseminates hematogenously in the lungs and/or systemically leading to miliary tuberculosis. Individuals who control the primary infection may undergo reactivation of the latent infection due to multiple factors including AIDS, malnourishment, alcoholism, and cancer. In these cases, reactivation can involve the lungs (cavitary, endobronchial, pneumonic, and/or bronchopneumonic) and other organs including the spleen, liver, bone marrow, kidneys, CNS, and bones. Primary and secondary mycobacterial resistance to antituberculosis medication in certain subpopulations in New York City and California makes tuberculosis a public health priority. Recent trends have shown that the percentage of isolates with resistance to antituberculosis drugs is decreasing due to vigorous public health efforts.

Viral Hemorrhagic Fevers (VHF)

It is estimated that 75% of EIDs in humans originate in animals, and VHFs are remarkable examples. The etiologic agents of this syndrome are a heterogenous group of RNA viruses belonging to three families, namely filoviruses (Ebola and Marburg viruses), arenaviruses (Lassa, Junin, Machupo, Guanarito, and Sabia viruses), and bunyaviruses (Crimean-Congo hemorrhagic fever and Rift Valley fever (RVF) viruses).

All these viruses have limited geographic ranges due to their specific natural reservoirs and vectors. In all cases, humans are accidental hosts. Pathogenetically, all VHFs lead to dramatically increased vascular permeability systemically with a hemorrhagic diathesis and edema in multiple organ systems, including the lungs and brain. These diseases all occur in localized outbreaks usually with very high case-fatality rates. Clinically, subtle differences exist between the syndromes such as more prominent hemorrhagic manifestations and terminal disseminated intravascular coagulation (DIC) in infections caused by filoviruses and CCHF, and prominent CNS and hemorrhagic manifestations in infections by the New World arenaviruses (Junin, Machupo, Sabia, and Guanarito), and prominent liver disease in RVF.

Rift Valley Fever

This is a mosquito-borne viral disease that affects newborn ruminants, especially sheep. Other affected animals include lambs, calves, goats, kittens, mice, and hamsters. The virus was first isolated in 1930 from sheep in Kenya, and the known distribution was limited to the African continent for decades. However, in 2000, a large epidemic in the Arabian peninsula led to high case-fatality ratios in humans, which had usually been around 5% in previous epidemics. Complications include hepatorenal failure, encephalitis and DIC leading to shock and multiorgan failure. The vector range for the virus is impressive and includes at least 30 species of mosquitoes in eight genera. Transovarial transmission occurs in the mosquitoes. Most outbreaks are related to climatic events that favor floods leading to increased vector populations. Outbreaks in Africa, besides the original one in Kenya, have occurred in Egypt (Aswan Dam construction), Mauritania in 1987 (Diama Dam construction), Kenya and Somalia in 1997–1998 (increased rainfall due to El Niño oscillation), and Kenya in 2007.

Ebola Hemorrhagic Fever (EHF)

Close to 20 outbreaks have occurred in Africa since Ebola virus was identified in 1976 in central Africa. The reservoir has been elusive although human outbreaks are usually preceded by severe primate die-offs. Recent studies of animals in the areas of primate mortality have identified bats as a likely reservoir host. Primary mechanisms of transmission from nonhuman primates to humans include contact with dead carcasses or handling or consumption of bushmeat. The virus has also been linked to lethal outbreaks in duikers, a wild ruminant. Other factors associated with EHF outbreaks include increases in rainfall. The viruses are rather stable genetically, since isolates obtained 20 years apart have limited genetic variation. The disease is rapidly progressive and leads to hemorrhagic manifestations very quickly.

South American Hemorrhagic Fevers

South American hemorrhagic fevers (HF) are caused by arenaviruses whose geographic distribution is limited. Most arenaviruses in Africa and the Americas do not cause human disease. Rodents develop a chronic infection that is most times asymptomatic but with

persistent viremia that can be lifelong. Vertical transmission occurs in mice. Both New World and Old World arenaviruses display a high specificity for their particular host. In the New World, reservoir rodents belong to the family Muridae, subfamily Sigmodontinae (rats and mice). Human infections occur via inhalation of aerosol particles containing infected urine from rodents. Ecologic factors associated with the emergence of these viruses as human pathogens include factors leading to increased rodent populations and increased contact between humans and rodents, e.g., deforestation and encroachment of farming into these areas. Human-to-human transmission is rare but can occur through contact with infected body fluids.

The New World viruses belong to the Tacaribe complex and include Junin (Argentine HF), Machupo (Bolivian HF), and Guanarito (Venezuelan HF) viruses. Few cases of HF due to Sabia virus (including two laboratory infections) have been described in Brazil, but the disease spectrum is largely unknown. Severe systemic disease with hemorrhage and prominent neurologic manifestations are the rule.

Dengue Fever

Dengue virus has been responsible for outbreaks of acute febrile illness (break-bone fever) in the tropics, and for the last 25 years, geographic expansion has occurred due to multiple environmental factors. In the United States, two large outbreaks occurred in Florida (1934) and New Orleans (1945). Four distinct dengue virus species are currently recognized, and the main vector is *Aedes aegypti*. The current geographic distribution ranges between 35° of latitude north and south. A prominent resurgence of dengue virus infections has occurred in the Caribbean basin, where the vector had been eradicated because of extensive campaigns against yellow fever. However, *A. aegypti* was reintroduced to the area, and large outbreaks of dengue fever (DF) and dengue hemorrhagic fever (DHF) have occurred in Cuba, Venezuela, Colombia, Central American countries, Mexico, and the Caribbean islands. A portion of dengue viral infections develop a life-threatening hemorrhagic fever.

EMERGING ENCEPHALITIC SYNDROMES

Nipah Virus Infection

This agent is a recently discovered paramyxovirus that, along with Hendra virus, comprises a new genus (*Henipavirus*) in the family Paramyxoviridae. In 1999, an outbreak of an acute febrile encephalitic syndrome in Malaysia was traced to Nipah virus. The epidemic was preceded by an epizootic of severe respiratory disease in pigs that was terminated after epidemiological control measures were instituted, including the culling of millions of pigs. A total of 283 cases of human encephalitis were diagnosed with a case-fatality rate close to 40%. A relapsing/remitting neurologic syndrome has also been associated with Nipah virus. A subsequent outbreak occurred in Bangladesh, but swine were not associated with this event, suggesting different ecological factors. The natural reservoir is thought to be fruit bats of the *Pteropus* genus. Other animals such as dogs, cats, and horses could also serve as hosts.

Hendra virus was first described in 1994 in Australia during a highly lethal epidemic of acute respiratory disease in horses. The only two human cases that have been associated with Hendra viruses manifested as acute respiratory syndrome and leptomeningitis, respectively. Both cases were fatal. The natural reservoir for Hendra virus is the fruit bat.

West Nile Virus (WNV) Infection

WNV was first isolated from humans in 1939 in Uganda and remained limited to the Middle East, Eastern Europe, and Africa until 1999, when an outbreak occurred in New York. By 2002, WNV spread across North America to the west coast, and annual outbreaks are now the rule. In 2002 and 2003, approximately 4000 and 9000 (case definition was modified in 2003) cases occurred, respectively, leading to CNS disease in 3000 and 2700 cases each year, respectively. Previous outbreaks of West Nile fever have occurred in Israel (1957), South Africa (1974), Algeria (1994), Tunisia (1997), and Congo (1998). WNV circulates enzootically between birds and mosquitoes. At least 300 species of birds and 62 species of mosquitoes can be infected by WNV. Most susceptible birds are the *Corvidae* (blue jays and crows), and the most important mosquito in the enzootic cycle is *Culex pipiens*. Humans and horses are dead-end hosts, both developing febrile and/or encephalitic syndromes. Other forms of transmission are through transplanted organs, transfusion, and breast milk. In fact, blood testing by PCR is now a component of the screening process for donated blood.

Prion Diseases (Transmissible Neurodegenerative Diseases)

Initially known as "atypically slow infections" (Sigurdsson, 1954), the concept of prion (proteinaceous

infectious agents) was first introduced by Prussiner in 1982. Currently a prion is known as "a small infectious pathogen that contains protein and is resistant to procedures that modify or hydrolyze nucleic acids." The pathogenesis of these diseases involves the generation and accumulation of abnormal prion protein from a normal isoform. The common denominator in these diseases in the presence of progressive neuronal degeneration (incubation periods measured in years or decades) accompanied by reactive astrocytosis and absence of inflammation. In most cases, prominent vacuolation of cells or neuropil is observed microscopically. Accumulation of abnormal prions in CNS tissue is present in all cases.

In humans, prions are responsible for several diseases of which Creutzfeldt–Jakob disease (CJD) and its new variant (linked to "mad cow disease" or bovine spongiform encephalopathy) are the most common. Other diseases include kuru, familial fatal insomnia (FFI), and Gerstmann–Straussler–Scheinker syndrome (GSS). CJD has several forms including sporadic (source of infection unknown), familial (mutations in the PrP gene), and iatrogenic (cadaveric grafts from patients with CJD). Kuru was related to anthropophagic practices in isolated tribes in Papua New Guinea, and new variant CJD has been linked to BSE. GSS and FFI are due to genetic mutations in the PrP gene in most cases.

ARTHROPOD TRANSMITTED BACTERIAL DISEASES

Lyme Borreliosis (Lyme Disease)

Lyme borreliosis is a zoonosis transmitted by hard ticks of the genus *Ixodes*. The vector in the eastern United States is *Ixodes scapularis* and in the western United States is *Ixodes pacificus*. *Ixodes ricinus* is the vector in Europe whereas *Ixodes persulcatus* is the vector in Russia and northern Asia. *B. burgdorferi* sensu lato includes *Borrelia burgdorferi* sensu stricto, *B. afzelii*, and *B. garinii*. The latter two are responsible for most cases of Lyme borreliosis in Europe, Russia, and northern Asia. Lyme disease has not been documented in tropical areas. The main hosts of *B. burgdorferi* in nature are rodents. Larval forms of ticks acquire the infection from small mammals, and the spirochetes are transmitted transtadially to nymphal and adult ticks. Human infections usually occur secondarily to nymph bites that go unnoticed very easily due to their small size.

Lyme borreliosis is a disease with an acute phase characterized by erythema migrans and nonspecific symptoms such as fever, headaches, myalgias, and arthralgias. The chronic phase (weeks to years) is characterized by oligoarthritis, central and peripheral nervous system sequelae, myocarditis, and other manifestations.

Rickettsioses

Rickettsia are obligately intracellular bacteria with a gram negative cell wall and a characteristic lipopolysaccharide. Their main target is the microvascular endothelium and different cells in their arthropod host/vector (fleas, ticks, lice, mites). Spotted fever group rickettsiae (with the exception of *Rickettsia felis* [fleas] and *Rickettsia akari* [mites]) are transmitted transovarially and transstadially in their tick vector and circulate in nature via small mammals. Fleas and lice host typhus group rickettsiae although they do not transmit the infection vertically to their offspring.

Newly described rickettsioses include *Rickettsia africae* (African tick bite fever), a closely related agent named *Rickettsia parkeri* (clusters of a relatively mild febrile disease in North and South America), *Rickettsia slovaca* (tick-borne lymphadenopathy or DEBONEL [*Dermacentor*-borne necrosis, eschar, lymphadenopathy]), *R. felis* (flea-borne spotted fever), *Rickettsia honei* (Flinders Island spotted fever), and *Rickettsia japonica* (Japanese spotted fever). The geographic distribution of these agents continues to expand. In fact, the distribution of organisms that appear to be variants of *R. japonica* now includes China and Korea. *R. honei* has been described in Thailand, and *R. felis* is probably distributed worldwide.

Ehrlichioses and Anaplasmosis

Obligately intracellular bacteria in the family Anaplasmataceae, which are related to the genus *Rickettsia*, include four human pathogens, *Ehrlichia chaffeensis* (human monocytotropic ehrlichiosis, HME), *Anaplasma phagocytophilum* (human granulocytotropic anaplasmosis, HGA), *Ehrlichia ewingii* (ehrlichiosis ewingii), and *Neorickettsia sennetsu* (mononucleosis-like illness in Japan). *N. sennetsu* is limited geographically to Japan, and its trematode host cycle differs greatly from the other pathogens in this family. The other three agents are tick-borne and have been considered until recently as veterinary pathogens. HME was first described in 1987, followed by HGA in 1994 and ehrlichiosis ewingii in 1999.

HME is predominantly transmitted by *Amblyomma americanum* ticks, and its main mammal reservoir in nature is the white-tailed deer (*Odocoileus virginianus*). Patients develop a febrile illness after a nymphal or

adult tick bite accompanied by headache, myalgias, malaise, and other nonspecific symptoms. A maculopapular skin rash is present in only 30–40% of cases. Common laboratory findings are the presence of leukopenia and/or thrombocytopenia during the acute phase of the disease. Complications include meningoencephalitis, hepatitis, and diffuse alveolar damage.

HGA is transmitted by *I. scapularis* ticks in the eastern United States and *I. ricinus* in Europe. The clinical picture is similar to HME although the case-fatality ratio and complications are less severe. The target cell of *A. phagocytophilum* is the polymorphonuclear neutrophil as compared with monocytes and macrophages for *E. chaffeensis*. The main reservoir in the eastern United States is the white footed mouse.

Ehrlichiosis ewingii caused by *E. ewingii* is the least known of the human ehrlichioses. It is transmitted by the same vector tick as *E. chaffeensis* and has a milder course. The target cell is the neutrophil. The majority of cases have been diagnosed in immunocompromised patients.

Scrub Typhus

A disease that ravaged American troops in the Pacific and Southeastern Asia during World War II is re-emerging in southern India, Sri Lanka, the Maldives, and Micronesia. The agent is *Orientia tsutsugamushi*, an obligately intracellular bacterium formerly known as *R.ickettsia tsutsugamushi*. The disease is transmitted by chiggers in their larval stage and occurs mostly in tropical Asia, the western Pacific islands, northern Australia, and temperate zones in Kashmir, Korea, Japan, and the lower Himalayas. In nature, wild rats maintain the chigger population (*Leptotrombidium* spp.), and *Orientia* is transmitted transovarially and transstadially. However, rats are not reservoirs for *O. tsutsugamushi*.

The disease is characterized by fever, headache, malaise, and a variable incidence of eschar formation at the bite site, lymphadenopathy, and a transient maculopapular rash. Severe manifestations include diffuse alveolar damage and meningoencephalitis. Poor responses to conventional treatments (tetracyclines and chloramphenicol) have been described in Thailand.

Bartonelloses

The genus *Bartonella* contains five recognized human pathogens: *B. bacilliformis* (Oroya fever and verruga peruana transmitted by sandflies of the genus *Lutzomyia*), *B. quintana* (trench fever, bacillary angiomatosis, and endocarditis transmitted by the human body louse, *Pediculus humanus corporis*), *B. henselae* (cat scratch disease, bacillary angiomatosis, and endocarditis transmitted by cat fleas and cats), and *B. elizabethae* and *B. vinsonii* (endocarditis, transmitted possibly by fleas and ticks).

The reservoir host for *B. bacilliformis* is humans who reside in endemic areas in Peru, Ecuador, and Colombia. Clinically the disease has an acute phase in which the main manifestation is severe hemolytic anemia followed by a chronic phase in which lesions composed of prominent capillary proliferations are present on the skin.

Trench fever affected millions of soldiers during World Wars I and II, and infections continue to be diagnosed worldwide especially in patients with HIV or malnourished, homeless alcoholics.

The feline ectoparasite flea *Ctenocephalides felis* is the vector of *B. henselae,* and humans acquire infection from contact with flea-infested cats. Endocarditis is a serious form of infection that can occur with *B. quintana*, *B. henselae*, *B. elizabethae*, and *B. vinsonii*. The epidemiology of the latter two infections is largely unknown.

EMERGING ENTERIC PATHOGENS

Cholera

Vibrio spp. are gram negative, oxidase positive, free-living bacteria found in warm, salty waters around the world. In these places, *Vibrio* is usually isolated from shellfish, and their concentration in the tissue is far greater than in the surrounding waters. *Vibrio cholerae*, *Vibrio vulnificus*, and *Vibrio parahemolyticus* are all associated with acute enteric infections in humans although the only one causing epidemics or pandemics is *V. cholerae*. The latter two are also associated with wound infections in warm salty waters or ingestion of raw shellfish with involvement of subcutaneous tissue and skeletal muscle and septicemia. Infections caused by *V. parahemolyticus* and *V. vulnificus* are more severe in immunocompromised patients and in persons with underlying diseases such as cirrhosis, hemochromatosis, and diabetes.

V. cholerae is classified by O antigens (>150), biotypes (classical and El Tor), and serotypes (Ogawa, Inaba). Six of the seven pandemics since the 19th century have originated in the Bengal basin, and the seventh pandemic began in 1961 in Indonesia. In 1991 this pandemic extended to Peru and other countries on the South American Pacific coast. In the US, the rare cholera cases have been linked to consumption of raw oysters or undercooked crab. All cases of *V. cholerae* infection were caused by O1 strains, but since

1992, 0139 strain has been isolated from clinical cases of cholera in the Indian subcontinent. Other non-O1 serogroups are sporadically associated with acute gastroenteritis around the world.

The majority of people infected with *V. cholerae* are asymptomatic or mildly ill (75% for the classical biotype and 93% for El Tor biotype). Presentation of the classic illness is explosive after a short incubation period (12 h–5 days) and consists of abundant watery diarrhea that leads to dehydration and circulatory collapse if not treated promptly.

Nontyphoidal Salmonelloses

In the United States, infections caused by nontyphoidal *Salmonella* spp. affect 1.4 million/year and kill approximately 600/year. Most patients are mildly symptomatic or asymptomatic. *Salmonella* are gram negative bacilli, nonlactose fermentors. The classification and nomenclature are extremely complex, but phylogenetic studies based on DNA sequencing reveal that *Salmonella* spp. associated with human illness are considered *Salmonella choleraesuis*, which has approximately 2500 serotypes including Typhimurium and Typhi. The name *Salmonella enterica* has been proposed to replace *S. choleraesuis*.

Virtually all cases of *Salmonella* infection are foodborne and are second only to enteric infections caused by *Campylobacter* spp. in the US. Foods associated with outbreaks in the US include undercooked ground beef, eggs, cheese, ice cream, fresh sprouts, juice, and other vegetables.

Clinical syndromes in nontyphoidal salmonellosis include gastroenteritis, bacteremia/septicemia with or without distant focal infections (infectious endarteritis in arteries with large atherosclerotic plaques, septic arthritis, and endocarditis) and asymptomatic carriage. Patients with immunosuppression of any etiology are at greater risk for systemic illness than immunocompetent patients.

Antimicrobial resistance (ampicillin, tetracyclines, chloramphenicol, streptomycin, and sulfonamides) in nontyphoidal salmonellosis is spreading throughout the world due to a specific phage infecting *Salmonella* type Typhimurium (DT104) that first appeared in 1990. Even more recently, resistance to fluoroquinolones and third and fourth generation cephalosporins has been reported.

Shiga-toxin Producing *Escherichia coli* Infection

The first human cases due to this organism were described in 1982 during two outbreaks of hemorrhagic colitis in the US due to *E. coli* serotype O157:H7. The association of hemorrhagic gastroenteritis due to O157:H7 and hemolytic uremic syndrome (microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia) was established soon thereafter. More than 30 serotypes of *E. coli* can produce *Shigella*-like toxins, but the vast majority of cases in the US are due to serotype O157:H7. The main vehicles of transmission are contaminated food (hamburgers, uncooked vegetables, and others), water, including swimming pools, person-to-person, and animal contacts.

Clinical presentation is rapid and includes vomiting, diarrhea, and cramping. The diarrhea becomes blood-streaked after a few days. One of the main complications is hemolytic uremic syndrome, mostly in patients under 5 years of age.

Helicobacter pylori Infection

The isolation of *H. pylori* (initially classified as *Campylobacter pylori* or *pyloridis*) from a human with active gastritis represents a turning point in how the medical field views peptic ulcer disease, acute and chronic gastritis, and gastric carcinoma (especially the intestinal variant). *H. pylori* is a motile, microaerophilic, gram negative bacillus capable of surviving in the harsh environment of the human stomach due to its microaerophilicity, capacity to penetrate the mucus layer overlying the gastric mucosa, and production of ammonia from urea via urease to neutralize the low pH in the environment. *H. pylori* infections seem to be limited to humans, but other *Helicobacter* spp. have been isolated from almost every mammal studied. Rates of infection in human populations are very high (in developing countries up to 70% by age 10 and nearly 100% by age 20), but clinical disease is not always apparent. Therefore, microbial and host factors are important in pathogenicity. The so-called *cag* pathogenicity island, the *vacA* gene, and their polymorphisms seem to play important roles in pathogenesis.

Human infections have been present for thousands of years based on studies of *H. pylori* alleles and human migrations. Once infection is acquired it persists for years or decades. Clinical syndromes associated with *H. pylori* infection include chronic diffuse superficial gastritis, intestinal metaplasia and atrophic gastritis, peptic, especially duodenal, ulcers (cagA-containing organisms), noncardiac gastric adenocarcinoma (cagA-containing bacteria), and gastric MALT-type B-cell lymphomas.

Cryptosporidiosis

Crysptosporidium parvum is a protozoan in the phylum Apicomplexa, class Sporozoae, subclass Coccidia.

Recent molecular studies have shown that *C. parvum* (the species thought to cause most human infections) contains various genotypes. In humans two genotypes cause infection: bovine and human genotypes. The name *Crysptosporidium hominis* has been proposed for the human genotype. The first human case was described in 1976, and the first outbreak of cryptosporidiosis in the US was documented in 1987 in Carroll County, GA where an estimated 13,000 cases of gastroenteritis were diagnosed. The largest reported outbreak occurred in Milwaukee, WI where there were an estimated 403,000 cases in 1993. *Cryptosporidium* has been described throughout the world. Infection occurs via the fecal–oral route mostly by ingestion of contaminated water. The infectious thick walled oocysts are resistant to chlorination and survive in moist environments for long periods of time. The cycle is completed in the same host, and multiplication is both sexual and asexual. Once inside the host, *Cryptosporidium* organisms invade the microvillous surface of the epithelial cells in the terminal ileum and proximal colon leading to self-limited watery diarrhea in immunocompetent patients and chronic/persistent diarrhea in immunocompromised patients (especially with AIDS).

Microsporidioses

Phylum Microsporidia are spore-forming, obligate intracellular protozoans that reside in the intestine, liver, kidneys, brain, and other tissues of wild and domesticated mammals and several other animal species. Eight genera out of more than 144 (containing more than 1000 species) have been documented as human pathogens which include *Encephalitozoon*, *Enterocytozoon*, *Pleistophora*, *Brachiola*, *Nosema*, *Trachipleistophora*, *Vittaforma*, and *Microsporidium*. The two most common species involved in humans are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. Microsporidioses, in general, are rare diseases in humans that have received attention due to the increased incidence of infections present in patients with AIDS.

Clinical syndromes in immunocompetent patients consist of self-limited diarrhea, ocular infections (keratitis), and meningoencephalitis. In immunocompromised patients (especially with AIDS), persistent watery diarrhea is the most common presentation. Severe CNS infections and disseminated infections have also been described including hepatitis, peritonitis, nephritis, and pneumonitis.

OTHER EMERGING BACTERIAL PATHOGENS

Diphtheria

Disease caused by infection with *Corynebacterium diphtheriae*, a gram positive, pleomorphic bacterium that was kept under good control in most parts of the world until 1990, re-emerged in the form of large epidemics in the former Soviet Union, extending into parts of Eastern Europe and Asia. The epidemic peaked in 1995 when 50,000 cases were reported in the Russian Federation. Vaccination lapses and disarray of the public health infrastructure are to blame for its reappearance. Humans are the only known reservoir of *C. diphtheriae,* and the primary route of spread is via respiratory droplets. Skin infection is less common. Asymptomatic pharyngeal carriers play an important role in maintaining the organisms in communities. The disease is mediated by a toxin encoded by a lysogenic phage. The toxin inhibits elongation factor 2 (EF2) in the ribosomes, thereby impairing protein synthesis. The main target organs are the nerves, heart, and kidneys. Before diphtheria was controlled in the mid-20th century, mainly infants were affected. However, in recent outbreaks young adults are more frequently affected, suggesting that infants in such populations are still somewhat protected.

Bordetella Infections

The main human pathogens in this group are *B. pertussis* (agent of whooping cough) and *B. parapertussis* (the agent of a milder form of whooping cough). Pertussis continues to be a public health problem worldwide with millions of cases reported every year. In the United States approximately 8000 cases occurred in 2002, affecting mostly adolescents and young adults. The disease seems to be largely underdiagnosed in these population groups, who are more susceptible than children because of lack of booster immunization for pertussis beyond childhood. Pertussis starts as an upper respiratory tract infection that progresses in a few days to paroxysmal cough that lasts for weeks or months. The bacterium is not invasive and remains in the respiratory tract. Secondary infections in the form of bacterial pneumonia can occur. Other complications include pneumothoraces, hernias, seizures, and otitis media.

Staphylococcus aureus Infections

This gram positive, aerobic coccus is one of the most ubiquitous microorganisms in human populations and is responsible for a wide spectrum of human diseases that range from simple skin "boils" to life-threatening generalized infections. In the last few decades, new clinical entities associated with *S. aureus* have emerged such as staphylococcal toxic shock syndrome (STSS), which is a potentially lethal disease mediated by a "superantigen" toxin (TSST-1) and is characterized by fever, hypotension, multisystem organ failure, and an erythematous rash that desquamates during recovery. TSST-1 is a nonspecific T-cell mitogen that leads to a dramatic increase of T-cells and subsequent increase in circulating cytokines. This syndrome was initially described in the setting of vaginal colonization by toxin-producing strains and use of superabsorbent tampons in 1978. This type of tampon was withdrawn from the market, and the incidence declined. However, nonmenstrual forms do exist and are associated with nasal packing, surgical wounds, and other focal *S. aureus* infections. A related condition present in neonates has been described recently in Japan and is known as neonatal toxic shock syndrome-like exanthematous disease.

Antibiotic resistance is a major problem in nosocomial infections due to *S. aureus*. Both methicillin-resistant and glycopeptide-resistant strains are a major threat in the hospital setting. *S. aureus* may be part of the normal flora, especially of the nares and skin. Other sites include the genitourinary tract, mucous membranes, GI tract, and upper respiratory tract. In fact, most infections are considered to be endogenous in origin.

Coagulase negative *Staphylococci* have also emerged as human pathogens in the setting of indwelling catheters and bioprosthetic devices. These bacteria are capable of forming extensive biofilms on inert surfaces leading to local or systemic infections.

GROUP A β-HEMOLYTIC STREPTOCOCCAL (GABHS) INFECTIONS

Streptococcus pyogenes Infections

This complex group of bacterial pathogens is responsible for a wide spectrum of infections in humans ranging from focal infections such as acute tonsillitis to the highly lethal streptococcal necrotizing fasciitis (better known as flesh-eating disease). The classification of *S. pyogenes* is based on antigenic properties and presence or absence of hemolysis on blood agar plates.

Classical diseases caused by this group of streptococci include its nonsuppurative complications (acute rheumatic fever and glomerulonephritis), tonsillitis, and scarlet fever. During the last two decades, GABHS have been associated with severe necrotizing fasciitis or streptococcal gangrene and streptococcal toxic shock syndrome. These conditions are associated with highly virulent streptococci capable of producing toxin superantigens (streptococcal pyrogenic exotoxins, SPE-A, SPE-B, and SPE-C) and other virulence factors capable of destroying host tissues. Fortunately, antibiotic resistance is not a major concern in infections caused by GABHS since the strains are still susceptible to most penicillin-related antibiotics. However, resistance to clindamycin and macrolides has been documented. Similar to *Staphylococci*, these organisms are part of the normal flora of multiple body sites including the skin, vagina, and pharynx.

Streptococcus agalactiae Infections

Group B streptococcal (*S. agalactiae*) infections have also emerged as a major cause of neonatal sepsis related to carriage of the bacterium in the vagina of pregnant women. Other conditions include focal and generalized infections in nonpregnant adults. Underlying conditions usually present in these patients are diabetes mellitus, neoplastic diseases, immobility, and chronic liver disease.

EMERGING CHRONIC VIRAL DISEASES

Acquired Immunodeficiency Syndrome

A pathogenic retrovirus infecting one of the most important cells orchestrating the acquired immune response in humans was something no scientist had in mind at the beginning of the 1980s. We now know that human immunodeficiency virus (HIV) infections were probably occurring sporadically for decades before the initial cases of HIV infection/AIDS were documented in the early 1980s. Unfortunately, HIV infection turns out to be one of the worst epidemics in modern history with more than 42 million people currently infected, most of whom live in sub-Saharan Africa (cumulative