Chapter 4

Emerging and Re-emerging Infectious Diseases

Emerging diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence (http://www3.niaid.nih.gov/research/topics/emerging).

Within the past two decades, innovative research and improved diagnostic and detection methods have revealed a number of previously unknown human pathogens. For example, within the past decade chronic gastric ulcers, which were formerly thought to be caused by stress or diet, were found to be the result of infection by the bacterium *Helicobacter pylori*.

New infectious diseases continue to evolve and "emerge." Changes in human demographics, behavior, land use, and so forth are contributing to the emergence of new diseases by changing transmission dynamics to bring people into closer and more frequent contact with pathogens. This may involve exposure to animal or arthropod carriers of disease.

As a result of innovative research and improved diagnostic and detection methods, a number of previously unknown pathogens—very often through host switching—have been identified as the causative agents of emerging and re-emerging diseases (www.niaid.nih.gov/dmid/eid/). For example, the increasing trade in exotic animals for pets and as food sources has contributed to the rise in opportunity for pathogens to jump from animal reservoirs to humans. For example, close contact with exotic rodents imported to the United States as pets was found to be the origin of the recent outbreak of monkeypox in the United States, and use of exotic civet cats for meat in China was found to be the route by which the SARS coronavirus made the transition from animal to human hosts (http://www3.niaid.nih.gov/research/topics/emerging).

In addition to the continual discovery of new human pathogens, old infectious disease enemies are "re-emerging." Natural genetic variations, recombinations, and adaptations allow new strains of known pathogens to appear to which the immune system has not been previously exposed and is therefore not primed to recognize (e.g., influenza). Furthermore, human behavior plays an important role in the re-emergence of diseases. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistant pathogens, allowing many diseases that were formerly treatable with drugs to make a comeback (e.g., tuberculosis, malaria, nosocomial infections, and food-borne infections). Recently, decreased compliance with vaccination policy has also led the to re-emergence of diseases, such as measles and pertussis, that were previously under control. The use of deadly pathogens, such as smallpox or anthrax, as agents of bioterrorism is an increasingly acknowledged threat to the civilian population. Moreover, many important infectious diseases have never been adequately controlled on either the national or international level. Infectious diseases that have posed ongoing health problems in developing countries are re-emerging in the United States (e.g., food- and water-borne infections, dengue, West Nile virus) (http://www3.niaid.nih.gov/research/topics/emerging).

4.1 Recent Outbreaks of Emerging and Re-emerging Infectious Diseases

Individual statistics for morbidity and mortality of emerging and re-emerging infections are difficult to determine because of their limited outbreaks. Current information on international outbreaks of infectious diseases can be obtained from WHO (http://www.who.int/csr/don/en/) and the CDC (http://www.cdc.gov/mmwr).

Recent outbreaks include:

- *Human Metapneumovirus (hMPV)*. HMPV was first identified in The Netherlands in 2001 in samples from children with respiratory tract disease *(1)*. It is a new member of the Paramyxoviridae family (subfamily Pneumovirus). Although newly discovered, hMPV is not thought to be a newly evolved virus because it was also found in Dutch blood samples dating back to the 1950s. Instead, it is believed that this pathogen has long been

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a common but undetected cause of many human respiratory illnesses. Moreover, it has been suggested that hMPV may be the second most common source of childhood respiratory infections after the respiratory syncytial virus (RSV), and its association with respiratory disease in adults and children has been reported in Canada, Australia, the United States, Hong Kong, Japan, and Finland. In addition, data from Hong Kong have indicated that half of the SARS patients tested during the recent outbreak were also co-infected with hMPV.

- *Borrelia hermsii*. A multicase tick-borne relapsing fever outbreak caused by *B. hermsii* has been reported in western Montana. *B. hermsii* is a pathogen closely related to the bacterium that causes Lyme disease, and its vector is *Ornithodoros hermsii (2)*. Though the tick-borne relapsing fever is endemic in the higher elevations and coniferous forests of the western United States and southern British Columbia, Canada, this is the first outbreak reported beyond the geographic range known previously in the United States. Patients usually become ill after sleeping in cabins infested with spirochete-infected ticks that feed quickly during the night.
- *Vibrio cholerae*. During spring 2002, a resurgence of cholera caused by *Vibrio cholerae* O139 was reported in Dhaka and adjoining areas in Bangladesh with an estimated 30,000 cases of cholera. The re-emerged O139 strains were found to belong to a single ribotype corresponding with one of two ribotypes that caused the initial O139 outbreak in 1993. This evidence suggested that the O139 strains continue to evolve and that the adult population continues to be more susceptible to O139 cholera, indicating the lack of adequate immunity against this serogroup *(3)*.
- *Norwalk-like Calciviruses (NLVs)*. The NLVs are an emerging group of pathogens of global importance that are frequently involved in food- and water-borne disease outbreaks. The human calciviruses belong to the genus Novovirus (NV) *(4)*. Whereas transmission of these viruses is primarily from person to person, numerous examples have illustrated that NVs are efficiently transmitted in food, water, or contaminated environmental surfaces *(5)*. Studies in which NVs were molecularly characterized have shown that numerous variants co-circulate in the community, but occasionally shifts did occur in which a single variant dominated over a wide geographic area *(6)*. During the period 1995–1996, a worldwide epidemic was observed *(7)*. The mechanism of emergence of these variants is unclear, but one hypothesis is that they represent widespread common-source events *(5)*.
- *Chikungunya*. Between March 28, 2005, and February 12, 2006, 1,722 cases of chikungunya have been reported in areas in the Indian Ocean, most notably in the French island of La Reunion *(8)*. Estimation from a mathematical model has indicated that as many as 110,000 people may have been infected by the chikungunya virus since March 2005. During the first week of February, other countries in the southwest Indian Ocean reported cases: Mauritius (206), the Seychelles (1,255 cases), and spreading further to Mayotte (France), India, China, and Europe. The disease is believed to have been first diagnosed in Tanzania in 1952 and then in Portklang in Malaysia in 1999. Warm and humid climate and water reservoirs serve as breeding grounds for chikungunya. The illness is considered to be a rare form of viral fever caused by an Alphavirus belonging to the group IV Togaviridae family *(9)*. The disease has a human-mosquito-human transmission. The mosquito vector is *Aedes aegyptii*. Chikungunya is not fatal but is associated with high morbidity (insomnia, severe headache, crippling joint and muscle pains) said to last for weeks. In a very recent development (September 6, 2007), the Ministry of Health of Italy confirmed about 160 cases of chikungunya in the Ravenna region of Northern Italy—the first reported outbreak of this tropical virus in Europe (http://news.bbc.co.uk/2/hi/health/6981476.stm).
- *Toxoplasma gondii*. Recently, several water-borne outbreaks of toxoplasmosis have been described *(10–15)*. Data from Brazil and North America have indicated that unfiltered drinking water contaminated with the parasite's oocysts is the main source of infection. However, transmission of toxoplasmosis has also resulted from consumption of food or water contaminated with oocysts from cat feces or soil or by eating undercooked meat that contained oocysts *(16, 17)*. In Latin America, seroprevalence of immunoglobulin G (IgG) to *T. gondii* was found to be generally high, ranging from 51% to 72% *(17)*.

4.2 Research Plans and Priorities

In response to the threat of emerging and re-emerging infectious diseases, NIAID has developed a strategy for addressing these issues through targeted research and training, initially outlined in 1999 in "A Research Agenda for Emerging Infectious Diseases" (http://www.niaid.nih.gov/publications/execsum/bookcover.htm), later updated in 2000 as "NIAID: Planning For the 21st Century" (http://www.niaid.nih.gov/strategicplan/pdf/splan.pdf), and in 2001 as "NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis" (http://www.niaid.nih.gov/publications/globalhealth/global.pdf). This document outlines the institute's plans for the next decade for diagnosing, treating, and preventing these three infections and also lays out a plan for enhancing research capacity in-country (http://www3.niaid.nih.gov/research/topics/emerging).

The NIAID research plans and priorities include:

- Strengthening basic and applied research on the pathogen, host, and environmental factors that influence disease emergence
- Using knowledge of pathogen, host, and environment interactions to enhance the ability to predict and prevent conditions that lead to human disease
- Supporting development of diagnostics, vaccines, and therapies necessary to detect and control infectious diseases
- Supporting sequencing and postgenomics research of emerging infectious disease agents and animal vectors to reveal the genetic basis for the microbe or vector's evolution, adaptation, and pathogenicity
- Developing new strategies to control diseases that are re-emerging due to drug or insecticide resistance
- Identifying better control strategies for intractable infectious diseases that continue to challenge global health
- Maintaining and developing the national and international scientific expertise required to respond to future health threats by supporting research and training programs

4.3 Resources for Researchers

4.3.1 New Research Facilities and Resources

NIAID is planning and has established several facilities and research programs to enhance research on emerging infectious diseases, including both naturally occurring outbreaks and those that may emerge as a result of deliberate release (acts of bioterrorism):

- *Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE)*. RCE will provide the scientific information and translational research capacity to make the next generation of therapeutics, vaccines, and diagnostics effective against emerging infectious agents, including the NIAID Category A–C Agents.
- *New NIAID Intramural Biosafety Level 3 (BSL-3) Laboratories*. These laboratories will enable the institute to conduct BSL-3 animal studies and laboratory research on emerging infectious agents, such as multidrug-resistant *Mycobacterium tuberculosis* (MDR TB), *Borrelia*, *Yersinia*, influenza virus, West Nile virus, and dengue virus
- *Two National Biocontainment Laboratories (NBL) and 13 Regional Biocontainment Laboratories (RBL)*. The NBLs and RBLs would provide Biosafety Level 3 and 4 facilities for biodefense and emerging infectious disease research.
- *NIAID's Biodefense and Emerging Infections Research Resources Program*. This program has been designed to support the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases.
- *The In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense Program*. This program provides a range of resources for preclinical testing of new therapies and vaccines including non-human primate models to be used in emerging infectious diseases and biodefense research.
- *The Food- and Water-borne Diseases Integrated Network*. This network expands the NIAID capacity to conduct clinical research studies of food- and water-borne enteric pathogens.

4.3.2 Other Resources

- *Malaria Research and Reference Reagent Resource (MR4) Center*
- *NIAID Animal Study Proposals*
- *Shiga Toxin Producing* Escherichia coli *(STEC) Strain and Data Repository*

4.4 List of NIAID Emerging and Re-emerging Diseases

Group I: Pathogens Newly Recognized in the Past Two Decades
Acanthamebiasis
Australian bat Lyssavirus
Babesia, atypical
Bartonella henselae
Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
Hendra or equine morbilli virus
Hepatitis C
Hepatitis E
Human herpesvirus 8
Human herpesvirus 6
Lyme borreliosis
Parvovirus B19

Group II: Re-emerging Pathogens
Enterovirus 71
Clostridium difficile

Coccidioides immitis
Mumps virus
Prion diseases
Streptococcus, group A
Staphylococcus aureus
Coccidioides immitis

Group III: Agents with Bioterrorism Potential

NIAID: Category A
Bacillus anthracis (anthrax)
Clostridium botulinum toxin (botulism)
Yersinia pestis (plague)
Variola major (smallpox) and other related pox viruses
Francisella tularensis (tularemia)
Viral hemorrhagic fevers:
Arenaviruses
LCM, Junin virus, Machupo virus, Guanarito virus
Lassa fever
Bunyaviruses: Hantaviruses; Rift Valley fever
Flaviviruses: Dengue
Filoviruses: Ebola and Marburg viruses

NIAID: Category B
Burkholderia pseudomallei
Coxiella burnetii (Q fever)
Brucella species (brucellosis)
Burkholderia mallei (glanders)
Chlamydia psittaci (Psittacosis)
Ricin toxin (from *Ricinus communis*)
Epsilon toxin of *Clostridium perfringens*
Staphylococcus enterotoxin B
Typhus fever (*Rickettsia prowazekii*)
Food- and water-borne pathogens:
Bacteria
Diarrheagenic *E. coli*
Pathogenic *Vibrio* species
Shigella species
Salmonella
Listeria monocytogenes
Campylobacter jejuni
Yersinia enterocolitica
Viruses (Calciviruses, hepatitis A)
Protozoa
Cryptosporidium parvum *Giardia lamblia*
Microsporidia *Entamoeba histolytica*
Toxoplasma *Cyclospora cayetanensis*
Additional viral encephalitides:
West Nile virus
La Crosse virus
California encephalitis
Venezuelan equine encephalomyelitis (VEE)
Eastern equine encephalomyelitis (EEE)
Western equine encephalomyelitis (WEE)
Japanese encephalitis virus
Kyasanur Forest virus

NIAID: Category C
Emerging infectious disease threats such as Nipah virus and additional hantaviruses

NIAID Priority Areas
- Tick-borne hemorrhagic fever viruses
  Crimean-Congo hemorrhagic fever virus
- Tick-borne encephalitis viruses
- Yellow fever
- Multidrug-resistant tuberculosis
- Influenza
- Other *Rickettsia* species
- Rabies
- Prions
- Chikungunya virus
- Severe acute respiratory syndrome–associated coronavirus (SARS-CoV)
- Antimicrobial resistance, excluding research on sexually transmitted organisms
- Antimicrobial research, as related to engineered threats
- Innate immunity, defined as the study of nonadaptive immune mechanisms that recognize, and respond to, microorganisms, microbial products, and antigens

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