Microbial Threats to Health: The Threat of Pandemic Influenza

Mark S. Smolinski, Margaret A. Hamburg, and Joshua Lederberg, Editors, Committee on Emerging Microbial Threats to Health in the 21st Century

ISBN: 0-309-65250-2, 48 pages, 6 x 9, (2005)

MICROBIAL THREATS TO HEALTH

THE THREAT OF PANDEMIC INFLUENZA

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The materials in this document draw from the 2003 Institute of Medicine publication, *Microbial Threats to Health: Emergence, Detection, and Response*, and have been updated with a new Preface by the committee chairs and study director.

Additional copies are available from the Institute of Medicine, 500 Fifth Street, NW, Washington, DC 20001. Copies of the full report, *Microbial Threats to Health: Emergence, Detection, and Response*, are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Adviser to the Nation to Improve Health

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

Preface

In 2003, the Institute of Medicine of the National Academies published a report, *Microbial Threats to Health: Emergence, Detection, and Response*, that addressed global emerging infectious diseases and provided a set of recommendations for responding to the threat. The recommendations called for enhancing global public health and medical response capacities, improving global infectious disease surveillance, rebuilding domestic public health capacity, encouraging better disease reporting, exploring innovative systems of surveillance, developing and using diagnostics, educating and training the public health and medical workforces, developing new vaccines and antimicrobial drugs, ending the inappropriate use of antimicrobials, improving vector and zoonotic disease control, and developing a comprehensive and interdisciplinary approach for addressing microbial threats to health.

It was no coincidence that the committee that authored the report chose to illustrate the report's cover with an artist's rendition of the ecology of influenza. The committee unanimously agreed that an influenza pandemic represented a significant threat to the world at the time of publication. Unfortunately, a mere two years later, we are indeed at the precipice of realizing the imminence of this threat. The World Health Organization has warned that mankind may never have faced a greater risk of a deadly epidemic than it is currently facing with influenza. Unless we take aggressive action now, an influenza pandemic will cause massive loss of life and economic disruption to any country and the world, either through the natural emergence of this threat or by the hands of man-made terror.

Influenza pandemics have appeared at irregular intervals during the last century, with the most devastating being the 1918 influenza pandemic that claimed more than 40 million lives worldwide in less than a year's time. The pandemic was especially brutal for those in early adulthood, something we do not routinely see with the annual influenza epidemics that tend to strike the very young or the very old. Scientists have been intrigued as to why the 1918 influenza strain was so lethal to those in the prime of their life, and the modern wonders of medical technology have made available the entire genomic sequence of that strain for research. Reverse genetic technology can remake this virus in the laboratory. While the advance of science may certainly provide insight to virulence factors of this historical strain and open new possibilities for antivirals and vaccines, we could put ourselves at risk from an inadvertent laboratory accident or even an intentional misappropriated use of this deadly strain as an agent of bioterrorism. While such apprehensions are the new reality of research in the biosciences, nature itself may be providing our greatest threat from a potentially virulent strain of influenza A, known as the H5N1 virus.

Influenza A (H5N1) is a subtype of the type A influenza virus. The virus is maintained in the environment by wild birds as the natural hosts, hence the name avian influenza or bird flu. The virus circulates among birds worldwide, is very contagious among them, and avian influenza epidemics can be deadly, particularly to domesticated birds like chickens. The world is witnessing such an event with the emergence of the H5N1 virus as the highly pathogenic strain that is responsible for the wide outbreak of avian influenza in the poultry populations of Asia.

The avian influenza virus does not typically infect humans with great efficiency; however, exposure to sick birds, uncooked poultry, or contaminated surfaces has been linked to the transmission of the H5N1 virus to humans. In 1997, the first direct bird-to-human transmission of influenza A (H5N1) virus was documented during an outbreak of avian influenza among poultry in Hong Kong. The H5N1 virus was responsible for at least 18 human cases of influenza disease and resulted in 6 deaths. This particular H5N1 virus was eradicated by culling all of the poultry in Hong Kong and was therefore not able to adapt to humans.

Since 1997, the world has witnessed highly pathogenic avian influenza, H5N1, in eight different countries simultaneously. Outbreaks of avian influenza occurred among poultry in Cambodia, China, Indonesia, Japan, Lao, South Korea, Thailand and Vietnam in 2003 and early 2004. At that time, more than 100 million birds either died from the disease or were culled. The massive culling of chickens is an important public health measure to prevent the spread of virus to humans. With increased incidence of sporadic bird-human transmission there is an elevated potential that avian and human influenza viruses will undergo genetic reassortment and poten-

tially emerge as a highly virulent strain that can be passed from human-to-human. An avian influenza epidemic also increases the possibility that this gene reassortment will occur in pigs, since they possess receptors for both avian and human influenza viruses.

According to the CDC, new research suggests that H5N1 viruses are becoming more capable of causing disease for mammals than earlier H5 viruses and are becoming more widespread in birds in the region. Other findings have documented H5 virus infection among pigs in China and Indonesia, and also in cats. These finding are particularly worrisome in light of the fact that reassortment of avian influenza genomes is most likely to occur when these viruses demonstrate a capacity to infect multiple species, as is now the case in Asia.

In early 2004, 35 confirmed human cases of H5N1 virus infection were reported in Thailand and Vietnam, resulting in 23 deaths. Beginning in late June 2004, new lethal outbreaks of H5N1 virus infection among poultry were reported in Cambodia, China, Indonesia, and for the first time, Malaysia. The new outbreaks in poultry were followed by renewed sporadic reporting of human cases of H5N1 virus infection in Vietnam and Thailand beginning in August 2004 and continuing into 2005. According to the World Health Organization, since January 2004, 97 cases and 53 deaths have been reported (as of May 12, 2005) in Viet Nam, Thailand and Cambodia. Viet Nam, with 76 cases and 37 deaths, has been the most severely affected country. It is important to note that no human cases have been isolated in Thailand in 2005.

It is now likely that H5N1 virus infection among birds has become endemic to Asia and human infections will continue to be reported. So far, no sustained human-to-human transmission of the H5N1 virus has been identified and no evidence for genetic reassortment between human and avian influenza virus genes has been detected. One instance of probable limited human-to-human transmission of H5N1 virus was reported in Thailand between a child and her mother and aunt in September 2004. In 2005, reports have been made of new family clusters of H5N1 virus infection in separate parts of Vietnam. If these H5N1 viruses gain the ability for efficient and sustained transmission between humans, an influenza pandemic could result with high rates of illness and deaths. It has been conservatively estimated that two to seven million deaths could occur worldwide. The current weight of evidence now suggests a shift from the possible to the likely.

In the event of an influenza pandemic of H5N1 virus, most of the world's population will have no humoral immunity to this strain. Our only defense will be the rapid development of an effective vaccine and/or the use of antivirals effective against the strain. In 2003, the Institute of Medicine Microbial Threats Committee reported, "Our nation—and the world—face

a serous crisis with respect to vaccine development, production, and deployment." This is as true for an influenza vaccine as it is for the vaccines needed to respond to the infectious diseases plaguing many parts of the globe on an annual basis. The reasons for this crisis are spelled out in the report and have been articulated in many other studies and reports from other organizations and governments. The bottom line is that the current technologies and infrastructure will require an estimated minimum of six months from the identification of the pandemic strain to the availability of a vaccine. Efforts to produce a vaccine that would be effective against the current strain of H5N1 virus are under way, but mass production and availability of such a vaccine is some time off.

This, in essence, leaves us with antivirals as our first line of defense. Of concern, genetic sequencing of H5N1 virus samples from human cases in Vietnam and Thailand show resistance to the antiviral medications amantadine and rimantadine, leaving only two remaining antiviral medications (oseltamavir and zanamavir) that should still be effective against currently circulating H5N1 virus strains. Again, despite numerous calls for the stockpiling of antivirals for influenza, we do not yet have in possession the adequate volume of antivirals necessary to respond to a pandemic.

The time to act is now. A number of immediate steps can be taken to prevent an inevitable influenza pandemic from reeking havoc upon the world. For years, pandemic influenza preparedness plans have been bantered around within nations and as a global plan. To answer the repeated call for a comprehensive strategy to respond to a pandemic, the political will to do so must be increased and must include governments, corporations, officials, health professionals, and the public. In the cases where action has occurred, it has not been enough or has not been of the scale that will be required to respond to the global demand that will follow a pandemic.

Although we are faced with a complex challenge of preparing for an influenza pandemic, we have the knowledge and capabilities to put in place systems to reduce the threat. Such systems can have vast implications for maintaining national and international security, and for saving lives. More needs to be done now, both within countries and globally, to better prepare for the threat of pandemic influenza. Renewed and serious commitments to the public/private partnerships are necessary for developing new vaccines for influenza and for assuring their adequate production and supply, whether for routine use or in a pandemic emergency. These same partnerships are also needed to contribute to the development of new and improved antivirals, and to ensure an adequate stockpiling of such drugs. The current global system for disease detection and reporting should be strengthened and expanded upon to get the earliest warning of an emerging outbreak, which is crucial to responding to a threat. Pandemic preparedness

plans should be in place on a local, national, and global level, to offer an effective plan to respond and to share critical resources during an unfolding crisis. And finally, we need to continue to work closely with other countries to develop new agricultural strategies and animal management practices that are less likely to propagate the development and rapid spread of influenza among animals, and more importantly, from animals to humans. These are just some of the key issues that must be approached from a global perspective if we are to be better prepared. Surely we do not want to be in the position of looking back after such an epidemic hits, wondering why we did not act before.

The public, scientific community, and policy makers must understand that the threat of an influenza pandemic is real and imminent. To this end, we have republished a section of the Microbial Threats report entitled: "Influenza: A Case in Point" in an effort to educate readers about the ecology of influenza and facilitate an informed response. In addition, we have included the executive summary of the report that has key information about the factors that lead to the emergence of microbial threats and the recommendations of the committee for implementing an effective and appropriate response.

We hope all citizens of the world, and especially our scientific and political leaders, will take it upon themselves to do all they can to act now to prevent and prepare for the global threat before us.

Sincerely,

Margaret A. Hamburg	Joshua Lederberg	Mark S. Smolinski
Co-chair and editor	Co-Chair and editor	Study Director and editor

Contents

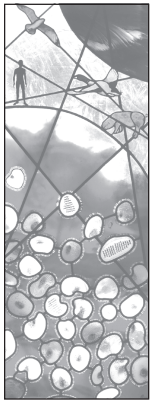
Executive Summary 1
Reprinted from *Microbial Threats to Health: Emergence, Detection, and Response* (2003)

A Case in Point: Influenza—We Are Unprepared 19
Reprinted from Chapter 3, pages 136-147 of *Microbial Threats to Health: Emergence, Detection, and Response* (2003)

References 31

Appendix 33

Reviewers 35



Executive Summary

Microbes live in every conceivable ecological niche on the planet and have inhabited the earth for many hundreds of millions of years. Indeed, microbes may be the most abundant life form by mass, and they are highly adaptable to external forces. The vast majority of microbes are essential to human, animal, and plant life. Occasionally, however, a microbe is identified as a pathogen because it causes an acute infectious disease or triggers a pathway to chronic diseases, including some cancers. Certainly, humankind remains ignorant of the full scope of diseases caused by microbial threats, as only a small portion of all microbes have been identified by currently available technologies.

Microbial threats continue to emerge, reemerge, and persist. Some microbes cause newly recognized diseases in humans; others are previously known pathogens that are infecting new or larger population groups or spreading into new geographic areas. Within the last 10 years, newly discovered infectious diseases have emerged in the United States (e.g., hantavirus pulmonary syndrome from Sin Nombre virus) and abroad (e.g., viral encephalitis from Nipah virus). During the same time, the worldwide resurgence of long-recognized infectious diseases (e.g., tuberculosis, malaria, cholera, and dengue) has gained in force. The United States has seen the importation of infectious diseases, such as West Nile encephalitis, measles, multidrug-resistant tuberculosis, malaria, and cyclosporiasis, from immigrants, U.S. residents returning from foreign destinations, and products of international commerce.

The realization of just how quickly newly discovered infectious diseases

can spread has generated a heightened appreciation of the inherent dangers of microbial pathogens. Acquired immunodeficiency syndrome (AIDS) has become the fourth-leading cause of death worldwide in a mere 20 years since its discovery. Today, more than 40 million people are living with infection from the human immunodeficiency virus (HIV), and 20 million people have died from AIDS. In just 3 years since West Nile virus was discovered in the Western Hemisphere, the virus has spread from its epicenter in New York to 39 states (including California), infecting thousands and killing hundreds.

The emergence and spread of microbial threats are driven by a complex set of factors, the convergence of which can lead to consequences of disease much greater than any single factor might suggest. Genetic and biological factors allow microbes to adapt and change, and can make humans more or less susceptible to infections. Changes in the physical environment can impact on the ecology of vectors and animal reservoirs, the transmissibility of microbes, and the activities of humans that expose them to certain threats. Human behavior, both individual and collective, is perhaps the most complex factor in the emergence of disease. Emergence is especially complicated by social, political, and economic factors—including the development of megacities, the disruption of global ecosystems, the expansion of international travel and commerce, and poverty—which ensure that infectious diseases will continue to plague us. Today we also face the threats of intentionally introduced biological agents. The risks to humankind from the willful spread of highly virulent and contagious microbes are considerable, and we in the United States are preparing to defend ourselves with new vaccines, diagnostics, and therapeutics against the many microbes that might be used in a biological attack. We also are cognizant of the need to rebuild public health infrastructure locally and globally as an indispensable means of reacting to such threats.

Can a focus on naturally occurring microbial threats be maintained in the face of expanded efforts to contain the threat of intentional biological attacks? Some may ask which is the greater risk—the intentional use of a microbial agent to cause sudden, massive, and devastating epidemics of disease, or the continued emergence and spread of natural diseases such as tuberculosis, AIDS, malaria, influenza, and multidrug-resistant bacterial infections. It is a tragic reality that hundreds of people die from naturally occurring infections every hour, whereas until now, intentional biological attacks on a major scale have remained a theoretical risk, rife with political as well as technical uncertainties. HIV/AIDS has taught us the importance of remaining vigilant to the devastation of naturally arising epidemics, which can have profound effects not only on individuals, but also on whole nations and regions. The economic and social disruption that often follows

an infectious disease outbreak and typically accompanies the persistent burden due to endemic infectious diseases can be a major destabilizing force for any nation. The challenge is to keep our concerns and responses in reasonable balance. This report contains prescriptions for acting wisely to integrate our surveillance, control, and prevention efforts aimed at natural scourges with enhanced security from intentional biological attacks.

Throughout history, humans have struggled to control both the causes and the consequences of infectious diseases, and we will continue to do so into the foreseeable future. Disease control for many pathogens includes vaccines and pharmaceuticals, but how long these controls will remain effective or even available is uncertain. We appear less able (or willing) to develop new antimicrobials and vaccines than once was the case, especially for infectious diseases that affect developing countries disproportionately. A variety of technical, political, social, and economic issues challenge our ability to develop and deploy new antimicrobials and vaccines. The burden of infectious diseases has become further compounded as resistance to vector-control agents and antimicrobials has grown pervasive not only in the United States, but also worldwide.

The 1992 Institute of Medicine report *Emerging Infections: Microbial Threats to Health in the United States* took a fresh look at the impact of new and reemerging infectious diseases on the United States. In 2001, the Committee on Emerging Microbial Threats to Health in the 21st Century was charged to identify, review, and assess the current state of knowledge regarding factors in the emergence of infectious diseases; to assess the capacity of the United States to respond to emerging microbial threats to health; and to identify potential challenges and opportunities for domestic and international public health actions to strengthen the detection and prevention of, and response to, microbial threats to human health. The committee acknowledges that infectious diseases in animals and agriculture have indirect effects on human health (e.g., reductions in available food sources, economic and psychological hardships for food-animal producers due to culling), and are an important component of the overall assessment of infectious disease response and control. The scope of this report, however, was limited to infectious diseases in humans.

SPECTRUM OF MICROBIAL THREATS

The spectrum of microbial threats is a continuum that comprises the emergence of newly recognized infectious diseases, the resurgence of endemic diseases, the appearance of new antimicrobial-resistant forms of diseases, the recognition of the infectious etiology of chronic diseases, and the intentional use of biological agents for harm.

FACTORS IN EMERGENCE

The convergence of any number of factors can create an environment in which infectious diseases can emerge and become rooted in society. A model was developed to illustrate how the convergence of factors in four domains impacts on the human–microbe interaction and results in infectious disease (see Figure ES-1). Ultimately, the emergence of a microbial threat derives from the convergence of (1) genetic and biological factors; (2) physical environmental factors; (3) ecological factors; and (4) social, political, and economic factors. As individual factors are examined, each can be envisioned as belonging to one or more of these four domains. The following individual factors in emergence are examined in this report:

Microbial adaptation and change. Microbes are continually undergoing adaptive evolution under selective pressures for perpetuation. Through structural and functional genetic changes, they can bypass the human immune system and infect human cells. The tremendous evolutionary potential of microbes makes them adept at developing resistance to even the most potent drug therapies and complicates attempts at creating effective vaccines.

Human susceptibility to infection. The human body has evolved with an abundance of physical, cellular, and molecular barriers that protect it from microbial infection. Susceptibility to infection can result when normal defense mechanisms are altered or when host immunity is otherwise impaired by such factors as genetically inherited traits and malnutrition.

Climate and weather. Many infectious diseases either are strongly influenced by short-term weather conditions or display a seasonality indicating the possible influence of longer-term climatic changes. Climate can directly impact disease transmission through its effects on the replication and movement (perhaps evolution) of pathogens and vectors; climate can also operate indirectly through its impacts on ecology and/or human behavior.

Changing ecosystems. In general, changes in the environment tend to have the greatest influence on the transmission of microbial agents that are waterborne, airborne, foodborne, or vector-borne, or that have an animal reservoir. Given today's rapid pace of ecological change, understanding how environmental factors are affecting the emergence of infectious diseases has assumed an added urgency.

Economic development and land use. Economic development activities can have intended or unintended impacts on the environment, resulting in eco-

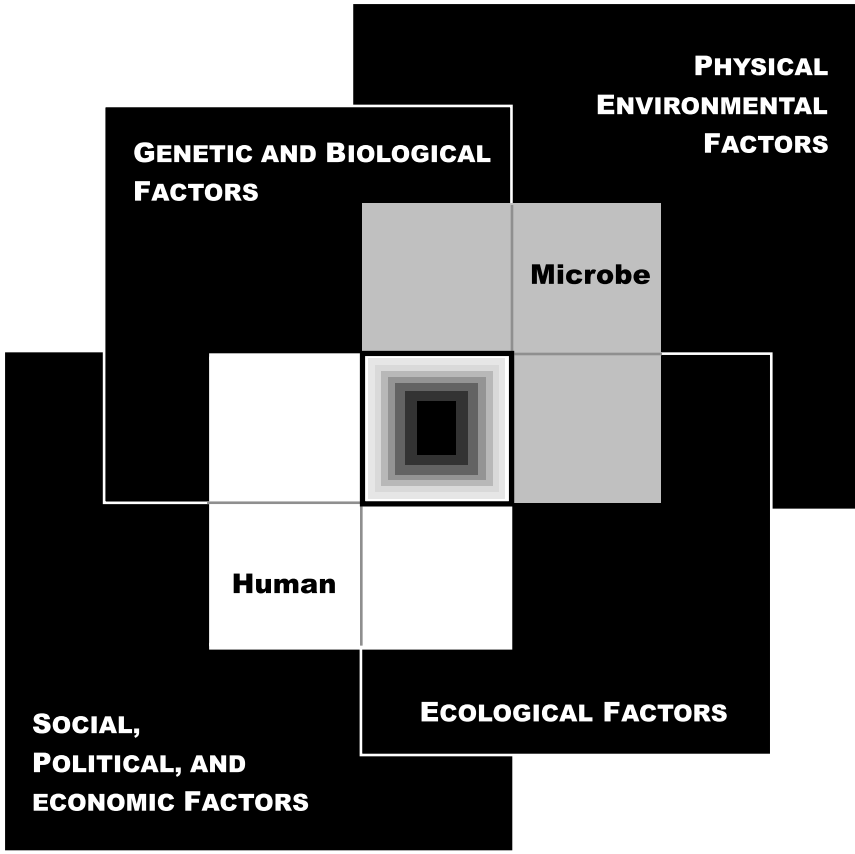


FIGURE ES-1 The Convergence Model. At the center of the model is a box representing the convergence of factors leading to the emergence of an infectious disease. The interior of the box is a gradient flowing from white to black; the white outer edges represent what is known about the factors in emergence, and the black center represents the unknown (similar to the theoretical construct of the "black box" with its unknown constituents and means of operation). Interlocking with the center box are the two focal players in a microbial threat to health—the human and the microbe. The microbe–host interaction is influenced by the interlocking domains of the determinants of the emergence of infection: genetic and biological factors; physical environmental factors; ecological factors; and social, political, and economic factors.

logical changes that can alter the replication and transmission patterns of pathogens. A growing number of emerging infectious diseases arise from increased human contact with animal reservoirs as a result of changing land use patterns.

Human demographics and behavior. An infectious disease can result from a behavior that increases an individual's risk of exposure to a pathogen, or from the increased probability of exchange of a communicable infectious disease between humans as the world's population increases in absolute number. Additional factors include demographic changes such as urbanization and the growth of megacities; the aging of the world's population and the associated increased risk of infection; and the growing number of individuals immunocompromised by cancer chemotherapy, chronic diseases, or infection with HIV.

Technology and industry. Infectious diseases have emerged as a direct result of changes in technology and industry. Advances in medical technologies, such as blood transfusions, human organ and tissue transplants, and xenotransplantation (using an animal source), have created new pathways for the spread of certain infections. Even the manner in which animals are raised as food products, such as the use of antimicrobials for growth production, has abetted the rise in infectious diseases by contributing to antimicrobial resistance.

International travel and commerce. The rapid transport of humans, animals, foods, and other goods through international travel and commerce can lead to the broad dissemination of pathogens and their vectors throughout the world. Microbes that can colonize without causing symptoms (e.g., *Neisseria meningitidis*) or can infect and be transmissible at a time when infection is asymptomatic (e.g., HIV, hepatitis B, and hepatitis C) can spread easily in the absence of recognition in traveling or migrant hosts. Pathogens in meat and poultry, such as the agents of "mad cow disease," can also be delivered unintentionally across borders, while the vectors of tropical diseases can be transported in cargo holds or in the wheel wells of international aircraft.

Breakdown of public health measures. A breakdown or absence of public health measures—especially a lack of potable water, unsanitary conditions, and poor hygiene—has had a dramatic effect on the emergence and persistence of infectious diseases throughout the world. The breakdown of public health measures in the United States has resulted in an increase in nosocomial infections, difficulties in maintaining adequate supplies of vaccines in recent years, immunization rates that are far below national targets for many population groups (e.g., influenza and pneumococcal immunizations in adults), and a paucity of needed expertise in vector control for diseases such as West Nile encephalitis.

Poverty and social inequality. At the same time that infectious diseases have

significant and far-reaching economic implications, social inequality, driven in large part by poverty, is a major factor in emergence. Mortality from infectious diseases is closely correlated with transnational inequalities in income. Global economic trends affect not only the personal circumstances of those at risk for infection, but also the structure and availability of public health institutions necessary to reduce risks.

War and famine. War and famine are closely linked to each other and to the spread of infectious diseases. Displacement due to war and the fairly consistent sequelae of malnutrition due to famine can contribute significantly to the emergence and spread of infectious diseases such as malaria, cholera, and tuberculosis.

Lack of political will. If progress is to be made toward the control of infectious diseases, the political will to do so must encompass not only governments in the regions of highest disease prevalence, but also corporations, officials, health professionals, and citizens of affluent regions who ultimately share the same global microbial landscape. The complacency toward the threat of infectious diseases that has become somewhat entrenched in developed countries must reverse in direction if we are to avoid losing windows of opportunity to reduce the global burden of infection.

Intent to harm. The world today is vulnerable to the threat of intentional biological attacks, and the likelihood of such an event is high. The U.S. public health system and health care providers should be prepared to address various biological agents that pose a risk to national security because of their potential to cause large numbers of deaths and widespread social disruption.

Recognizing and addressing the ways in which the factors in emergence converge to change vulnerability to infectious diseases is essential to the development and implementation of effective prevention and control strategies. Detecting and responding to global infectious disease threats is in the economic, humanitarian, and national security interests of the United States and essential to the health of its people.

ADDRESSING THE THREATS: CONCLUSIONS AND RECOMMENDATIONS

The response to a microbial threat—from detection to prevention and control—is a multidisciplinary effort involving all sectors of the public health, clinical medicine, and veterinary medicine communities. The committee's recommendations emerged from focused deliberations and applica-

tion of the criteria of urgency, priority, and amenability to immediate action. Given that infectious diseases are a significant threat to the health of the world's population, several of the committee's recommendations could be justified solely on the basis of humanitarian need; *all* are justified as being in the best interest of the United States to protect the health of its own citizens.

Enhancing Global Response Capacity

Infectious diseases are a global threat and therefore require a global response. Nations not only must be concerned about the endemic diseases that plague their own citizens, but also must expand their concerns to include the global burden of disease that ultimately encompasses the gamut of potential threats—even if these threats are not currently found within their borders. While the true burden of infectious diseases in many areas of the world is unknown, the greatest burden occurs within developing countries, where an estimated one in every two persons dies from such a disease. The United States' capacity to respond to microbial threats must therefore include a significant investment in the capacity of developing countries to monitor and address microbial threats as they arise.

The United States should seek to enhance the global capacity for response to infectious disease threats, focusing in particular on threats in the developing world. Efforts to improve the global capacity to address microbial threats should be coordinated with key international agencies such as the World Health Organization (WHO) and based in the appropriate U.S. federal agencies (e.g., the Centers for Disease Control and Prevention [CDC], the Department of Defense [DOD], the National Institutes of Health [NIH], the Agency for International Development [USAID], the Department of Agriculture [USDA]), with active communication and coordination among these agencies and in collaboration with private organizations and foundations. Investments should take the form of financial and technical assistance, operational research, enhanced surveillance, and efforts to share both knowledge and best public health practices across national boundaries.

Improving Global Infectious Disease Surveillance

Global surveillance, especially for newly recognized infectious diseases, is crucial to responding to and containing microbial threats before isolated outbreaks develop into regional or worldwide pandemics.

The United States should take a leadership role in promoting the implementation of a comprehensive system of surveillance for global infec-

tious diseases that builds on the current global capacity of infectious disease monitoring. This effort, of necessity, will be multinational and will require regional and global coordination, advice, and resources from participating nations. A comprehensive system is needed to accurately assess the burden of infectious diseases in developing countries, detect the emergence of new microbial threats, and direct prevention and control efforts. To this end, CDC should enhance its regional infectious disease surveillance; DOD should expand and increase in number its Global Emerging Infections Surveillance (GEIS) overseas program sites; and NIH should increase its global surveillance research. In addition, CDC, DOD, and NIH should increase efforts to develop and arrange for the distribution of laboratory diagnostic reagents needed for global surveillance, transferring technology to other nations where feasible to ensure self-sufficiency and sustainable surveillance capacity. The overseas disease surveillance activities of the relevant U.S. agencies (e.g., CDC, DOD, NIH, USAID, USDA) should be coordinated by a single federal agency, such as CDC. Sustainable progress and ultimate success in these efforts will require health agencies to broaden partnerships to include nonhealth agencies and institutions, such as the World Bank.

Rebuilding Domestic Public Health Capacity

Strong and well-functioning local, state, and federal public health agencies working together represent the backbone of an effective response to infectious diseases. The U.S. capacity to respond to microbial threats is contingent upon a public health infrastructure that has suffered years of neglect. Upgrading current public health capacities will require considerably increased, sustained investments.

U.S. federal, state, and local governments should direct the appropriate resources to rebuild and sustain the public health capacity necessary to respond to microbial threats to health, both naturally occurring and intentional. The public health capacity in the United States must be sufficient to respond quickly to emerging microbial threats and monitor infectious disease trends. Prevention and control measures in response to microbial threats must be expanded at the local, state, and national levels and be executed by an adequately trained and competent workforce. Examples of such measures include surveillance (medical, veterinary, and entomological); laboratory facilities and capacity; epidemiological, statistical, and communication skills; and systems to ensure the rapid utility and sharing of information.

Improving Domestic Surveillance Through Better Disease Reporting

Open lines of communication and good working relationships among health care providers, clinical laboratories, and public health authorities are essential to robust systems of surveillance and effective implementation of disease investigation and response activities. The reporting of infectious diseases by health care providers and laboratories, however, remains inadequate.

CDC should take the necessary actions to enhance infectious disease reporting by medical health care and veterinary health care providers. Innovative strategies to improve communication between health care providers and public health authorities should be developed by working with other public health agencies (e.g., the Food and Drug Administration [FDA], the Health Resources and Services Administration [HRSA], USDA, the Department of Veterans Affairs [VA], state and local health departments), health sciences educational programs, and professional medical organizations (e.g., the American Medical Association, the American Society for Microbiology, the American Nurses Association, the American Veterinary Medical Association, the Association for Professionals in Infection Control and Epidemiology, the Association of Teachers of Preventive Medicine).

CDC should expeditiously implement automated electronic laboratory reporting of notifiable infectious diseases from all relevant major clinical laboratories (e.g., microbiology, pathology) to their respective state health departments as part of a national electronic infectious disease reporting system. The inclusion of antimicrobial resistance patterns of pathogens in the application of automated electronic laboratory reporting would assist in the surveillance and control of antimicrobial resistance.

Exploring Innovative Systems of Surveillance

The ability to gather and analyze information quickly and accurately would improve the nation's ability to recognize natural disease outbreaks, track emerging infections, identify intentional biological attacks, and monitor disease trends. Surveillance systems within the United States, however, remain fragmented and have not evolved at the same rate as the electronic technological advances that could significantly improve the timeliness and integration of data collection.

Research on innovative systems of surveillance that capitalize on advances in information technology should be supported. Before widespread implementation, these systems should be carefully evaluated for their usefulness in detection of infectious disease epidemics, including their potential for detection of the major biothreat agents, their ability to monitor the spread of epidemics, and their cost-effectiveness. Research on syndromic surveillance systems should continue to assess such factors as the capacity to transmit existing data electronically, to standardize chief complaint or other coded data, and to explore the usefulness of geospatial coding; CDC should provide leadership in such evaluations. In addition, promising approaches will need to be coordinated nationally so that data can be shared and analyzed across jurisdictions.

Developing and Using Diagnostics

Etiologic diagnosis—identifying a microbial cause of an infectious disease—is the cornerstone of effective disease control and prevention efforts, including surveillance. Etiologic diagnosis has declined significantly over the past decade. A dangerous consequence of decreased etiologic diagnosis has been an increase in the inappropriate use of broad-spectrum antibiotics and the emergence of antimicrobial resistance. Improving etiologic diagnosis would be of value to human health worldwide in directing appropriate therapy, as well as informing disease surveillance and response activities.

CDC and NIH should work with FDA, other government agencies (e.g., DOD, USDA, the national laboratories), and industry on the development, assessment, and validation of rapid, inexpensive and cost-effective, sensitive, and specific etiologic diagnostic tests for microbial threats of public health importance.

Public health agencies and professional organizations (e.g., those concerned with patient care, health education, and microbiological issues) should promulgate and publicize guidelines that call for the intensive application of existing diagnostic modalities and new modalities as they are established. Such guidelines should be incorporated into continuing education programs, board examinations, and accreditation practices. Payers for health care should cover diagnostic tests for infectious diseases to increase specific diagnoses and thereby inform both public health and medical care, including monitoring of inappropriate use of antimicrobials.

Educating and Training the Microbial Threat Workforce

The workforce necessary to accomplish the needed improvement in the national capacity to respond to microbial threats must be supported with strong training programs in the applied epidemiology of infectious disease prevention and control. As a vital component of this workforce, the knowledge and skills needed to confront microbial threats must be better integrated into the training of all health care professionals to ensure a prompt and effective response to any and all infectious disease threats, whether naturally occurring or maliciously introduced.

CDC, DOD, and NIH should develop new and expand upon current intramural and extramural programs that train health professionals in applied epidemiology and field-based research and training in the United States and abroad. Research and training should combine field and laboratory approaches to infectious disease prevention and control. Federal agencies should develop these programs in close collaboration with academic centers or other potential training sites. Domestic training programs should include an educational, hands-on experience at state and local public health departments to expose future and current health professionals to new career options, such as public health.

Vaccine Development and Production

Our nation—and the world—faces a serious crisis with respect to vaccine development, production, and deployment. Concern has increased over the inadequacy of vaccine research and development efforts, periodic shortages of existing vaccines, and the lack of vaccines to prevent diseases that affect persons in developing countries disproportionately. Yet, too little has been done to resolve these issues. The evolving threat of intentional biological attacks makes the need for focused attention and action even more critical.

The challenges associated with vaccine innovation, production, and deployment are many and complex. Solutions will require a novel, coordinated approach among government agencies, academia, and industry. Issues that must be examined and addressed in a more meaningful and systematic fashion include the identification of priorities for research, the determination of effective incentive strategies for developers and manufacturers, liability concerns, and streamlining of the regulatory process. Currently, the federal government is neither addressing all of these challenges at a sufficiently high level nor providing adequate resources. Leadership, empowerment, and accountability are urgently needed at the cabinet level to

ensure a comprehensive, integrated vaccine strategy that will address the following critical elements:

The U.S. Secretary of Health and Human Services should ensure the formulation and implementation of a national vaccine strategy for protecting the U.S. population from endemic and emerging microbial threats. Only by focusing leadership, authority, and accountability at the cabinet level can the federal government meet its national responsibility for ensuring an innovative and adequately funded research base for existing and emerging infectious diseases and the development of an ample supply of routinely recommended vaccines. The U.S. Secretary of Health and Human Services should work closely with other relevant federal agencies (e.g., DOD, the Department of Homeland Security, VA), Congress, industry, academia, and the public health community to carry out this responsibility.

The U.S. Secretary of Defense, the U.S. Secretary of Health and Human Services, and the U.S. Secretary of Homeland Security should work closely with industry and academia to ensure the rapid development and deployment of vaccines for naturally occurring or intentionally introduced microbial threats to national security. The federal government should explore innovative mechanisms, such as cooperative agreements between government and industry or consortia of government, industry, and academia, to accelerate these efforts.

The Administrator of USAID, the U.S. Secretary of Health and Human Services, and the U.S. Secretary of State should work in cooperation with public and private partners (e.g., leaders of foundations and other donor agencies, industry, WHO, UNICEF, the Global Alliance for Vaccines and Immunization) to ensure the development and distribution of vaccines for diseases that affect populations in developing countries disproportionately.

Need for New Antimicrobial Drugs

Drug options for treatment of infections are becoming increasingly limited, largely as a result of growing antimicrobial resistance. Many generic but essential antibiotics are in short supply, and the development of new antibiotics has been severely curtailed. In the past three decades, only two new classes of antibiotics have been developed, and resistance to one class emerged even before the drugs entered the commercial market. Only four large pharmaceutical companies with antibiotic research programs

remained in existence in 2002 and not one new class of antibiotics is in advanced development. Likewise, antivirals for only a limited number of viral diseases are available, and few are in development. In the event of a natural or intentionally introduced microbial threat, antimicrobials may be the only available first line of response. A readily available supply, therefore, should be a priority of preparedness plans.

The U.S. Secretary of Health and Human Services should ensure the formulation and implementation of a national strategy for developing new antimicrobials, as well as producing an adequate supply of approved antimicrobials. The U.S. Secretary of Health and Human Services should work closely with other relevant federal agencies (e.g., DOD, the Department of Homeland Security), Congress, industry, academia, and the public health community to carry out this responsibility.

The U.S. Secretary of Health and Human Services and the U.S. Secretary of Homeland Security should protect our national security by ensuring the stockpiling and distribution of antibiotics, antivirals (e.g., for influenza), and antitoxins for naturally occurring or intentionally introduced microbial threats. The federal government should explore innovative mechanisms, such as cooperative agreements between government and industry or consortia of government, industry, and academia, to accelerate these efforts.

Inappropriate Use of Antimicrobials

The world is facing an imminent crisis in the control of infectious diseases as the result of a gradual but steady increase in the resistance of a number of microbial agents to available therapeutic drugs. The problem is of global concern and is creating dilemmas for the treatment of infections in both hospitals and community health care settings. Moreover, as noted above, the pharmaceutical industry is developing fewer new antimicrobials than in previous years. Therefore, immediate action must be taken to preserve the effectiveness of available drugs by reducing the inappropriate use of antimicrobials in human and animal medicine.

CDC, FDA, professional health organizations, academia, health care delivery systems, and industry should expand efforts to decrease the inappropriate use of antimicrobials in human medicine through (1) expanded outreach and better education of health care providers, drug dispensers, and the general public on the inherent dangers associated with the inappropriate use of antimicrobials, and (2) the increased use

of diagnostic tests, as well as the development and use of rapid diagnostic tests, to determine the etiology of infection and thereby ensure the more appropriate use of antimicrobials.

FDA should ban the use of antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans.

Vector-Borne and Zoonotic Disease Control

Vector-borne and zoonotic diseases remain major causes of morbidity and mortality in humans living in tropical climates, and represent a large portion of newly emerged diseases worldwide. Vector-borne and zoonotic pathogens have the ability to spread rapidly across broad geographical areas, as evidenced by the spread of West Nile virus across the United States. Exacerbating the situation is the potential for many vector-borne and zoonotic agents to be weaponized and used by terrorists. The national and international capacity to address these diseases must be strengthened by rebuilding the workforce and infrastructure, and developing the tools necessary to respond appropriately to such threats.

CDC, DOD, NIH, and USDA should work with academia, private organizations, and foundations to support efforts at rebuilding the human resource capacity at both academic centers and public health agencies in the relevant sciences—such as medical entomology, vector and reservoir biology, vector and reservoir ecology, and zoonoses—necessary to control vector-borne and zoonotic diseases.

DOD and NIH should develop new and expand upon current research efforts to enhance the armamentarium for vector control. The development of safe and effective pesticides and repellents, as well as novel strategies for prolonging the use of existing pesticides by mitigating the evolution of resistance, is paramount in the absence of vaccines to prevent most vector-borne diseases. In addition, newer methods of vector control—such as biopesticides and biocontrol agents to augment chemical pesticides, and novel strategies for interrupting vector-borne pathogen transmission to humans—should be developed and evaluated for effectiveness.

CDC, DOD, and NIH should work with state and local public health agencies and academia to expand efforts to exploit geographic information systems (GIS) and robust models for predicting and preventing the emergence of vector-borne and zoonotic diseases.

Comprehensive Infectious Disease Research Agenda

To ensure that the United States is strategically poised to protect itself against the threat of infectious diseases and to maximize its assistance in global efforts to combat these diseases, further investments must be made to support a diverse array of multidisciplinary research domains. These new investments must be part of an overall strategy for improved public health preparedness and protection against infectious disease threats. A comprehensive system of accountability must be in place to ensure that no critical areas are neglected. Given that the emergence of infectious diseases is the result of a complex convergence of factors, it is clear that multidisciplinary studies are greatly needed.

NIH should develop a comprehensive research agenda for infectious disease prevention and control in collaboration with other federal research institutions and laboratories (e.g., CDC, DOD, the U.S. Department of Energy, the National Science Foundation), academia, and industry. This agenda should be designed to investigate the role of genetic, biological, social, economic, political, ecological, and physical environmental factors in the emergence of infectious diseases in the United States and worldwide. This agenda should also include the development and assessment of public health measures to address microbial threats. A sustained commitment to a robust research agenda must be a high priority if the United States is to dramatically reduce the threat of naturally occurring infectious diseases and intentional uses of biological agents. The research agenda should be flexible to permit rapid assessment of new and emerging threats, and should be rigorously reevaluated on a 5-year basis to ensure that it is addressing areas of highest priority.

Interdisciplinary Infectious Disease Centers

As noted, addressing the highly complex nature of infectious disease emergence requires the involvement of experts from a broad range of disciplines and health sectors. The present structure of academic and public health institutions, however, requires that most of these arenas operate independently of each other. Opportunities for collaboration and synergism will be enhanced if experts convene under the same roof (or on the same campus) to discuss a problem, thus avoiding lost opportunities for collaboration and reducing often unnecessary redundancies of effort and expense. Furthermore, an interdisciplinary, collaborative approach can facilitate the training of the workforce needed to address the problems of emerging microbial threats facing the world today.

Interdisciplinary infectious disease centers should be developed to promote a multidisciplinary approach to addressing microbial threats to health. These centers should be based within academic institutions and link (both physically and virtually) the relevant disciplines necessary to support such an approach. They would collaborate with the larger network of public agencies addressing emerging infectious diseases (e.g., local and state health agencies, CDC, DOD, the U.S. Department of Energy, FDA, the Food Safety and Inspection Service, NIH, the National Science Foundation, USAID, USDA), interested foundations, private organizations, and industry. The training, education, and research that these centers would provide are a much-needed resource not only for the United States, but also for the entire world.

CONCLUSION

Today's world is truly a global village, characterized by growing concentrations of people in huge cities, increasing global commerce and travel, progressive damage to natural ecosystems, poverty, famine, and social disruption. One can safely predict that infectious diseases will continue to emerge, and that we will encounter unpleasant surprises, as well as increases in already worrisome trends. Depending on present policies and actions, this situation could lead to a catastrophic storm of microbial threats.

Thus while dramatic advances in science and medicine have enabled us to make great strides in our struggle to prevent and control infectious diseases, we cannot fall prey to an illusory complacency. We must understand that pathogens—old and new—have ingenious ways of adapting to and breaching our armamentarium of defenses. We must also understand that factors in society, the environment, and our global interconnectedness actually increase the likelihood of the ongoing emergence and spread of infectious diseases. It is a sad irony that today we must also grapple with the intentional use of biological agents to do harm, human against human.

No responsible assessment of microbial threats to health in the twenty-first century, then, could end without a call to action. The magnitude and urgency of the problem demand renewed concern and commitment. We have not done enough—in our own defense or in the defense of others. As we take stock of our prospects with respect to microbial threats in the years ahead, we must recognize the need for a new level of attention, dedication, and sustained resources to ensure the health and safety of this nation—and of the world.

A CASE IN POINT: INFLUENZA—WE ARE UNPREPARED*

The factors that underlie the emergence of all infectious diseases are expanding in magnitude and converging at an ever more rapid pace, thus increasing individual and societal vulnerability to infection. Not only do individual factors lead to the emergence of infectious diseases, but the convergence of factors in time and space can lead to effects greater than the summing of individual factors might predict. Recognition of a convergence of factors can provide warning of an impending microbial threat, and an impetus to *act* now rather than simply *react* after an infection has become rooted in society. A better understanding of how the factors involved in emergence can converge to change vulnerability to infectious diseases would allow better preparedness for the prevention and control of microbial threats to health.

Humanity's struggle with influenza is illustrative of such a convergence of factors, which has resulted in maintaining the presence of this virus and periodically led to epidemics of the disease. Social, political, and economic factors interact with ecological factors to drive influenza viruses to respond through biological and genetic factors, thus circumventing human defense mechanisms and, in today's increasingly global society, exerting effects on economic, social, and political life worldwide (see Figure 3-1 for a visual model of this convergence of factors). The challenges to the prevention and control of influenza as a natural threat illuminate the ultimate challenge of addressing the convergence of factors that led to its emergence in the first place. Indeed, influenza is the paradigm of a microbial threat to health in which continual evolution of the virus is the main mechanism underlying epidemic and pandemic human disease. The gene pool of influenza A viruses in wild aquatic birds provides all the genetic diversity required for the emergence of new strains of pandemic influenza in humans, lower animals, and birds. A new influenza pandemic in humans is inevitable, and despite the development of pandemic plans in several countries, including the United States, we remain poorly prepared.

Epidemics and Pandemics

The highly variable nature of influenza virus permits the microbe to escape immune responses generated by previous infections and to cause annual epidemics and occasional pandemics of disease in humans (Wright

*Reprinted from Chaper 3, "Factors in Emergence" (pp. 136-147), *Microbial Threats to Health: Emergence, Detection, and Response,* (2003).

BOX 3-20
The 1918 Influenza Pandemic

The 1918 influenza A pandemic claimed more than 20 million lives worldwide in less than a year and ranks among the worst disasters in human history. In the United States alone, it is estimated that 1 in 4 people became ill during the pandemic and that 675,000 people died.

Doubt remains as to whether the 1918 influenza pandemic originated in the United States, China, or France. There is agreement that a mild wave occurred simultaneously in the United States, Europe, and Asia in March–April 1918. It is postulated that genetic changes in that virus resulted in high pathogenicity in the second wave. The second wave occurred in September–November 1918 and affected one-quarter of the world's population; 500 million people were clinically affected during the pandemic.

The name Spanish flu came not from major outbreaks in Spain, but from high mortality among troops in France that for intelligence reasons were attributed to Spanish origins. The highest mortality from the disease occurred after the arrival of American troops in France. Indeed, General Erich Ludendorff, the Imperial German Army Chief of Staff, concluded that it was the virus, not the fresh troops, that ended the World War. A remarkable feature of the 1918 pandemic was that deaths were highest among young adults in the 20–40 year age range.

Molecular analysis of the hemagglutinin (HA), neuraminidase (NA), and nonstructural genes from formalin-treated lung samples in paraffin blocks from soldiers that died in the second wave and from lung tissue from an Inuit woman buried in the permafrost in Alaska has provided information on the probable origin of the virus (Taubenberger et al., 2001). Phylogenetic analysis of the complete HA and NA sequences supports the hypothesis that the 1918 virus was derived from avian influenza precursors and was most closely related to classical swine influenza virus. To date, however, this analysis provides no insight into the enormous pathogenicity of the virus.

The return of military personnel throughout the world coincided with the peak of the second wave. In many cities, the disease was so severe that coffins were stacked in the streets, and the impact was so profound that it depressed the average life expectancy in the United States by more than 10 years. In spring 1919, a nasty but less lethal third wave occurred, and substantial mortality also recurred in 1920 (Kilbourne et al., 1987).

The complete sequence of the 1918 virus will be resolved in the near future, and reverse genetics technology is in place to remake this virus. If we wish to understand the molecular basis of high pathogenicity, remaking the virus may be the only option. If this is done, great care must be exercised to use the highest level of biosecurity. The available sequence information on the HA would permit us to make vaccines, and the sequence of the NA indicates sensitivity to the neuraminidase inhibitors. The precursor virus(es) of the 1918 virus still exist in nature and there is nothing to prevent it or a virus of similar virulence from reemerging (Taubenberger et al., 2001).

and Webster, 2001). The severity of the epidemics ranges from mild to severe; on average, in nonpandemic years influenza causes 20,000 deaths in the United States. At irregular intervals—three to four times per century—human pandemics of influenza arise. The most devastating of these in recent history, the "Spanish flu" of 1918 (see Box 3-20), caused more than 20 million deaths worldwide and affected more than 200 million people. In only a few months, it killed more people than had been killed in battle during the 4 years of World War I (1914 to 1918). Viruses descended from the pandemic strain continued to cause annual epidemics from 1920 to 1956. The "Asian flu" pandemic (caused by an H2N2 virus) killed approximately 70,000 persons in the United States. The most recent pandemic, the 1968 "Hong Kong flu," killed approximately 34,000 persons in the United States. Thus, a pattern is evident: each pandemic is followed by relatively mild yearly epidemics caused by related viruses for which the populace enjoys widespread immunity. After a time, however, the evolving influenza virus gene pool inevitably produces a strain to which humans have no immunity. If we are unlucky, it is a highly transmissible and lethal strain.

Disturbingly, in 1977 an H1N1 virus similar in all respects to a virus from 1957 reappeared in humans in Northern China. This virus was not highly lethal—in fact, it caused only moderate respiratory illness in persons under 20 years of age. The cause of great concern was the possibility that this virus could have come from a frozen source, released accidentally from a laboratory. This event raises the specter of the reappearance of H2N2 influenza viruses that have been stored since the pandemic of 1957. No one born after 1957 has high-level immunity to these viruses, and the biosecurity of such agents is a matter of increasing concern. It has now been more than 30 years since a new pandemic influenza virus has emerged. The world's influenza advisory groups have warned that a new pandemic is not only inevitable, but overdue.

Impact of Influenza on Society and the Economy

The social and economic impacts of influenza are most apparent during a pandemic. During the lethal wave of the 1918 Spanish flu pandemic (October–November 1918), cities throughout the world were unable to bury their dead; in undeveloped areas, entire villages perished. The social and economic burden of influenza during interpandemic periods is less well studied, especially in tropical areas where malaria and diarrheal diseases remain major problems. However, studies in Canada, the United States, and Holland have shown that annual epidemics of influenza have a major impact on hospital costs among children and the elderly and reduce productivity. Indeed, after evaluating the economic impact of interpandemic influenza, several countries have recommended the annual use of influenza vac-

cine. In the United States, this recommendation has been extended to all persons aged 50 years or older and those at high risk because of underlying diseases or immunosuppression. The province of Ontario, Canada, has made the most progress in this respect; in 2002, vaccination was offered free of charge to everyone over 6 months of age. In other provinces of Canada, vaccination is still recommended for those aged 65 and older and for all high-risk groups. Broader vaccination has not been pressed in the United States, purportedly because of limited supplies of vaccine. The result is a vicious cycle, however, as manufacturers will not produce quantities in excess of the certain demand.

Genetic and Biological Factors

Microbial Adaptation and Change

Influenza virus is ideally designed for continuous evolution. Its highly variable antigenic domains, which are situated at the outer end of the spike glycoproteins, permit maximal variability without compromising the function or assembly of the virion (see Figure 3-10) (Lamb and Krug, 2001). The virus's genome comprises eight RNA segments that can be shuffled or reassorted in cells that are coinfected with multiple viruses. Because of the lack of proofreading mechanisms, influenza virus undergoes an extremely high rate of mutation as it replicates (approximately 1.5×10^{-5} mutations per nucleotide per replication cycle). To cope with the continual genetic variation of human influenza viruses, WHO has established a worldwide network of more than 100 laboratories that isolate viruses for antigenic and molecular analysis (Cox and Subbarao, 2000). These analyses form the basis of WHO's annual recommendations for influenza vaccines for the Northern and Southern Hemispheres.

Unlike influenza viruses in humans, influenza viruses in their natural aquatic bird reservoirs appear to be in evolutionary stasis (Webster et al., 1992). Some avian influenza viruses have shown no changes in their surface glycoproteins for more than 50 years. The RNA continues to undergo mutation, but the mutations provide no selective advantage; these influenza viruses have become perfectly adapted to their natural hosts over the course of time. After transfer to a new host, however, the viruses evolve rapidly, undergoing a high rate of nonsynonymous mutation that alters their amino acid structure.

The existence of five host-specific lineages of influenza (in humans, horses, pigs, domestic poultry, and sea mammals) indicates that aquatic avian influenza viruses have adapted to these species, overcoming differences between avian and mammalian hosts in body temperature, cell surface receptors, and mode of transmission (see Figure 3-11). In aquatic birds,

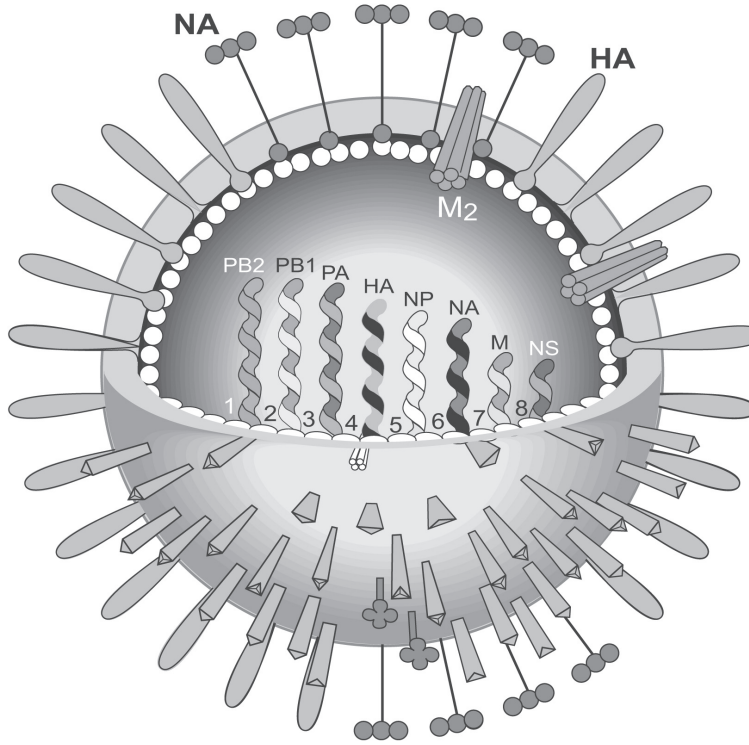


FIGURE 3-10 Diagram of influenza virus. The surface of the influenza virus particle is comprised of three kinds of spike glycoproteins—the hemagglutinin (HA) that attaches the viruses to sialic acid residue on the respiratory tract; neuraminidase (NA), an enzyme that releases the influenza virus from infected cells and is the target of the anti-neuraminidase drugs; and matrix (M2) protein, which is an ion channel and is the target for the antiviral agents amandatine and rimantadine. The spike glycoproteins are embedded in a lipid bilayer obtained from the host cell. The inside of the lipid bilayer is lined by the matrix protein (M1). A core of the virus contains eight single-stranded RNA segments of negative sense that permits genetic mixing (reassortment) when two different viruses infect a single cell. The polymerase complex (PB2, PB1, PA, NP) is involved in viral replication. The two smallest segments (M and NS) each encode two proteins in different reading frames. The NS gene is important in regulating the host cell response to influenza virus infection.

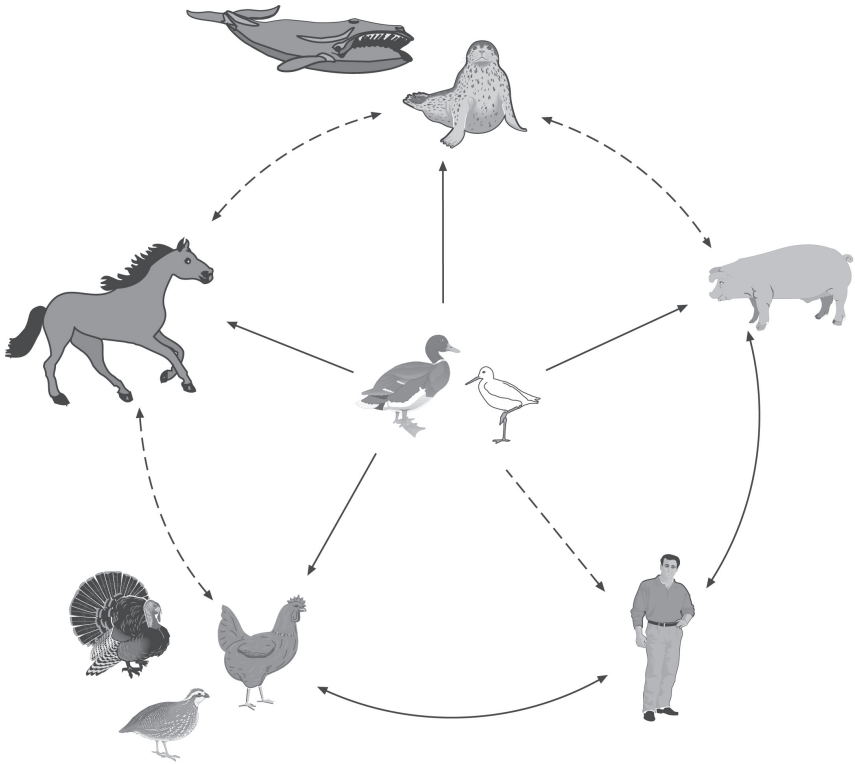


FIGURE 3-11 The reservoir of influenza A viruses. The working hypothesis is that wild aquatic birds are the primordial reservoir of all influenza viruses for avian and mammalian species. Transmission of influenza has been demonstrated between pigs and humans and between chickens and humans but not between wild birds and humans (dotted lines). There is extensive evidence for transmission of influenza viruses between wild ducks and other species (solid lines). The five different host groups are based on phylogenetic analysis of the nucleoprotein genes of a large number of different influenza viruses.

influenza virus is an enteric parasite that is transmitted by ingestion of fecally contaminated water. In humans, the virus replicates in the respiratory tract and is transmitted via aerosol. The available evidence suggests that the avian–human transition is accomplished via infection of pigs. Pigs possess receptors for both avian (α 2–3 terminal sialic acid) and human (α 2–6 terminal sialic acid) influenza viruses and thus can act as intermediate hosts. In this respect, it is noteworthy that both the 1918 Spanish and the 1968 Hong Kong pandemic viruses were isolated from pigs and from

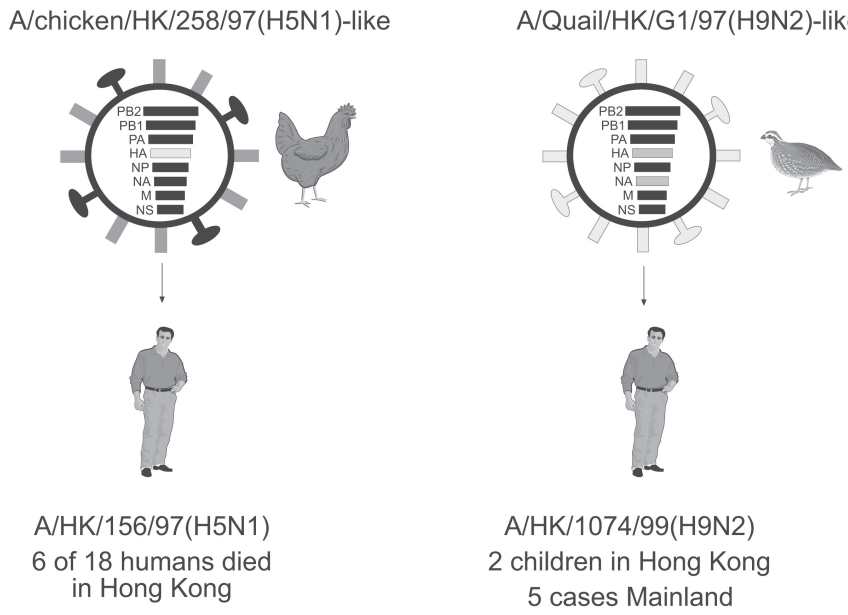


FIGURE 3-12 Direct transmission of avian influenza viruses to humans. In 1997, avian influenza viruses transmitted directly to humans in Hong Kong killed 6 of 18 persons(Left). In 1999, a quail influenza virus transmitted to humans in Hong Kong and caused mild respiratory infection in two children (Right). Five additional cases of H9N2 influenza have been reported from humans in Mainland China. It is noteworthy that the two influenza viruses from avian species that infected humans contain identical internal genes (PB2, PB1, PA, NP, M, NS—black gene segments) suggesting that these gene segments contain unique regions that facilitated transmission to humans.

humans at approximately the same time. The interspecies transmission of influenza usually results only in transitory, localized disease that may be mild to severe. The H5N1 "bird flu" incident in Hong Kong in 1997 was such an incident. Six of eighteen infected persons died, but a stable lineage was not established (see Figure 3-12). The possibility that the virus might adapt to humans, however, was sufficiently disquieting to prompt the wholesale slaughter of poultry in Hong Kong on two occasions.

During and after adaptation of influenza viruses to a new host, a continuing battle for supremacy occurs between microbe and host. The innate and adaptive human immune responses battle to clear the virus, while the virus evolves strategies to circumvent the immune responses. The virus stays a few steps ahead of natural or vaccine-induced human immunity by means of antigenic drift, or the accumulation of amino acid substitutions in

the antigenic epitopes on the spike glycoproteins (hemagglutinin [HA] and neuraminidase [NA]) to which neutralizing antibodies bind. Genetic shift, or the acquisition of new gene segments from the aquatic bird reservoir, can completely change the epitopes that evoke humoral and cell-mediated immunity. This phenomenon may explain in part the devastation wreaked by the 1918 Spanish flu pandemic. The microbe has also developed ways to downregulate the innate immune response. One of the nonstructural proteins of influenza A viruses (NS1) is an interferon agonist that downregulates interferon—a natural inhibitor of influenza viruses (Garcia-Sastre, 2002). The yearly epidemics of influenza attest to the ongoing battle between host and virus. Human interventions—vaccines and antivirals—are efficacious on an individual basis, but have had little effect on the global spread of the disease.

Two classes of antivirals are used against influenza viruses: the adamantines, which block the ion channel formed by the influenza matrix (M2) protein, and the neuraminidase inhibitors, which prevent virus release by blocking NA enzyme activity (Hayden, 2001). The virus is able to circumvent these antivirals through the natural selection of resistant mutants. Resistance to the adamantines emerged in the first patients who were treated. However, the microbe has had less success in developing resistance to the NA inhibitors. Resistance to these agents requires mutations in both HA and NA, and the NA mutation compromises transmission of the virus. Thus, resistance can be achieved only at a price to the virus.

In summary, the challenges presented by influenza virus reflect its ability to alter itself with remarkable rapidity. This characteristic allows it to survive, to adapt to new hosts, and to evade control strategies.

Human Susceptibility to Infection

The most severe influenza virus infection experienced by most humans is the first infection acquired after the decline of maternal antibodies; the outcome depends on the competency of the individual's immune function and on the pathogenic potential of the specific variant of influenza virus. Patients who are immunosuppressed because of disease or therapy may shed influenza virus for long periods, and a greater likelihood exists in these individuals that the virus will acquire resistance to natural immune mechanisms and to antiviral therapy. The pathogenicity of influenza virus strains may also differ among host groups. Young adults were most susceptible in the 1918 pandemic, despite peak immune competence at that age. The future may reveal that the virus was able to downregulate the host immune response through as-yet unrecognized mechanisms.

Pacific Island communities also appeared to differ in their susceptibility to the 1918 Spanish flu. The death rate among the Maori population in

New Zealand was 43.3 per 1,000 people—almost six times the death rate among New Zealanders of European extraction. Socioeconomic factors account for some but not all of this difference. Other possible factors include the absence of previous exposure of the Maori population to any influenza virus.

The main preventive human defense mechanism against influenza virus infection is humoral immunity (i.e., antibodies) to the highly variable HA and NA spike glycoproteins of the virus. To recover from influenza infection and remove infected cells, on the other hand, the body depends on cell-mediated immunity. Thymus-derived lymphocytes (T cells) recognize specific antigenic epitopes on the viral nucleoprotein and polymerase proteins, and they cross-react with these epitopes on other influenza virus strains. Both types of specific immune response require prior exposure to the virus. Therefore, an immune-naïve child, who has developed neither humoral nor cell-mediated immunity to the virus, may have a severe respiratory infection. On exposure to a second influenza virus that is antigenically similar to the first but has undergone antigenic drift, the child will be infected but will recover more rapidly because of the cross-reactive cell-mediated immune response. However, there is a conundrum associated with the immune response to highly variable microbes. The child's second exposure to influenza virus will induce a response directed mainly against the *first* influenza virus encountered. In this phenomenon, known as original antigenic sin, the immune system retains a lifelong memory of the first virus exposure in childhood. Thus, the antibody response is misdirected, and the efficacy of humoral immunity is reduced. This mechanism affects immunity to all infectious agents that undergo antigenic drift, including HIV.

Ecological Factors

Fifteen HA and nine NA subtypes of influenza A viruses circulate in the aquatic birds of the world. The viruses cause no apparent disease in these natural hosts, with which they appear to be in near-perfect equilibrium (Webster et al., 1992). Phylogenetically, these viruses can be divided into two clades, one in the Americas and the other in Eurasia. To date, only three of the fifteen HA subtypes have established lineages in humans. It is possible that only those subtypes have the capacity to infect humans. However, the direct transmission of avian H5N1 and H9N2 influenza viruses to humans in Hong Kong in 1997 and 1999 suggests the possibility that all subtypes can infect humans. The adaptation of influenza viruses to wild aquatic birds that migrate over vast distances (e.g., from southern South America to the North Slopes of Alaska) is an evolutionary strategy that allows the widespread fecal dissemination of the viruses at no apparent cost

to the host. It is only after transmission and adaptation to mammals or domestic poultry that the virus evolves into a disease-causing microbe.

Social, Political, and Economic Factors

Animal Husbandry, Human Behavior, and Travel

The human population of the world continues to increase, as does the number of animals required to feed it. China has seen the most dramatic rise in the number of animals over the past decade. The demand for meat protein has increased strikingly as the result of socioeconomic progress, and populations of pigs and chickens have grown exponentially. Zoonotic disease potential inevitably increases in proportion to the animal population. Poultry, pigs, and people are the known hosts of influenza viruses, and most of the influenza pandemics of the twentieth century have originated in China. Substantial influenza activity has been noted in Hong Kong, which is hypothesized to be a documentable epicenter for the emergence of influenza pandemics. In 1997, avian H5N1 influenza virus was transmitted directly from poultry to humans, killing six of eighteen infected persons. In 1999, avian H9N2 influenza viruses were transmitted to two children and caused mild respiratory disease (see Figure 3-12). In 2001 and 2002, H5N1 viruses that are highly pathogenic to poultry and to mammals (as shown by testing in mice) reappeared in Hong Kong. To prevent spread to humans of the 2001/H5N1 viruses, all of the poultry in Hong Kong was killed and buried. Since 2001, all poultry markets in Hong Kong have been emptied on the same day each month to reduce the buildup of virus. Despite these precautions, however, all of the elements are in place to generate a new pandemic: vast numbers of the primary and secondary susceptible hosts on the mainland and in Hong Kong, and a constantly evolving pathogen. It is inevitable that an influenza pandemic strain will emerge from this mix.

However, the purchase of live poultry is a long-standing tradition, and thousands of people are employed in that industry. A change to the Western-style sale of chilled or frozen slaughtered poultry will meet with resistance until health authorities and the public recognize the ultimate cost of a new pandemic in Asia. Technical and political factors are also at work. The wide availability of refrigeration has now rendered the live poultry markets obsolete, but cultural preferences remain a strong political impediment to regulatory change. As a long-term solution, live poultry markets should be closed not only in Asia, but also in New York City. The markets in New York City are a factor in the emergence of the H7N2 influenza viruses that are causing great losses in the poultry industry in the northeastern United States. More than 4 million birds have had to be slaughtered, and the disease outbreak has prompted a ban on U.S. poultry in Japan.

Besides the live markets, close monitoring of other crowded flocks of poultry will be needed.

Modern air travel (discussed earlier) will inevitably hasten the spread of a new pandemic of influenza. Once the virus appears in a major urban area, modern travel will allow its global distribution within a matter of days. The economic impact of an outbreak of highly pathogenic influenza was clearly seen in Hong Kong in 1997. The tourist and poultry industries collapsed because of the H5N1 "bird flu" incident, and Hong Kong suffered a severe economic downturn.

Intent to Harm

Recent advances in reverse genetics of influenza viruses now make it possible to generate influenza viruses to order (Neumann and Kawaoka, 2001). This new technology can reduce the time needed for vaccine preparation by 1 to 2 months if all other necessary resources are available. Perhaps more important, it will allow us to discover the molecular basis of the lethality of some viruses, such as the 1918 Spanish flu pathogen, and identify new targets for intervention in both the microbe and the host. Unfortunately, this new knowledge will also make it possible to generate extremely deadly agents—to recreate the 1918 Spanish flu virus, for example, or to add the H5N1 bird flu genes to a human influenza strain. Although influenza is not high on the list of bioterrorism agents, it has the potential to wreak widespread havoc on human life or to devastate important agricultural resources. Influenza is an exemplar of nature's natural biowarfare; it now has the added potential to be used by humans for intentional harm.

Pandemic Preparedness

Influenza is not an eradicable disease. It has now been more than 34 years since the Hong Kong/68 (H3N2) pandemic, and, as noted, all influenza virologists agree that a new pandemic is imminent. All of the developed countries of the world and WHO have created influenza pandemic plans to deal with such an event, and WHO is in the process of developing a Global Agenda for Influenza. Key issues in the global agenda are improvement of global surveillance, assessment of the global burden of influenza, and acceleration of vaccine development and usage.

The disturbing reality is that despite the certainty of a pandemic, even the developed countries of the world are quite unprepared for such an event. The public health infrastructure is inadequate. Hospitals lack the capacity to accommodate a surge of patients. Vaccine manufacturers had severe problems in meeting the demand in 2001 and 2002, the mildest

influenza years in two decades, and the repertoire of antiviral drugs is completely inadequate. And increasing bacterial resistance to antibiotics raises questions about our ability to deal effectively with secondary pneumonia, a common cause of influenza deaths.

If a country cannot cope with interpandemic influenza, it is likely that the pandemic, when it does occur, will cause massive societal disruption. Such disruption cannot be prevented, but it can be lessened if we take action now. A minimum of 6 months is needed to prepare a new influenza vaccine. Only 11 companies worldwide manufacture influenza vaccine, and all of these companies together could not prepare a sufficient quantity even for national, let alone global needs. Therefore, the only immediately available strategy in the face of an influenza pandemic is the use of antivirals. Supplies of these agents are currently tailored to meet very low demand, and it takes an estimated 18 months to manufacture significant quantities of the drugs from the starting materials. Therefore, anti-influenza drugs will be available only if they are stockpiled in advance of a pandemic. Modeling studies are needed to plan the most effective use of such a stockpile of drugs.

The steps needed to deal effectively with interpandemic influenza can also help in preparing for an influenza pandemic. The new initiative promoting universal influenza vaccination in Ontario, Canada, can serve as a model for the world. If demonstrated to be effective, it should be expanded to other areas. Unless vaccine usage is substantially increased during interpandemic years, vaccine manufacturing capacity will be inadequate to meet the demand generated by a pandemic.

REFERENCES

Cox NJ, Subbarao K. 2000. Global epidemiology of influenza: past and present. *Annu Rev Med* 51:407-21.

Garcia-Sastre A. 2002. Mechanisms of inhibition of the host interferon alpha/beta-mediated antiviral responses by viruses. *Microbes Infect* 4(6):647-55.

Hayden FG. 2001. Perspectives on antiviral use during pandemic influenza. *Philos Trans R Soc Lond B Biol Sci.* 356(1416):1877-84.

Kilbourne ED, Cerini CP, Khan MW, Mitchell JW Jr, Ogra PL. 1987. Immunologic response to the influenza virus neuraminidase is influenced by prior experience with the associated viral hemagglutinin. I. Studies in human vaccines. *J Immunol* 138(9):3010-3.

Lamb RA, Krug RM. 2001. Orthomyxoviridaw: the viruses and their replication. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. Philadelphia: Lippincott Williams & Wilkins.

Taubenberger JK, Reid AH, Janczewski TA, Fanning TG. 2001. Integrating historical, clinical and molecular genetic data in order to explain the origin and virulence of the 1918 Spanish influenza virus. *Philos Trans R Soc Lond B Biol Sci* 356(1416):1829-39.

Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. 1992. Evolution and ecology of influenza A viruses. *Microbiol Rev* 56(1):152-79.

Wright PF, Webster RG. 2001. Orthomyxoviruses. In: Knipe DM, Howley PM, eds. *Fields Virology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins. Pp. 1533-79.

APPENDIX

COMMITTEE ON MICROBIAL THREATS TO HEALTH IN THE 21ST CENTURY

MARGARET A. HAMBURG (Co-chair), Vice President for Biological Programs, Nuclear Threat Initiative

JOSHUA LEDERBERG (Co-chair), Professor Emeritus and Sackler Foundation Scholar, The Rockefeller University

BARRY BEATY, Professor of Microbiology, Colorado State University

RUTH BERKELMAN, Professor, Department of Epidemiology, Rollins School of Public Health, Emory University

DONALD BURKE, Professor, Departments of International Health and Epidemiology, Bloomberg School of Public Health, Johns Hopkins University

GAIL CASSELL, Vice President of Scientific Affairs and Distinguished Research Scholar in Infectious Diseases, Eli Lilly and Company

JIM YONG KIM, Co-director of program in Infectious Disease and Social Change, Department of Medicine, Harvard University

KEITH KLUGMAN, Professor of International Health, Department of International Health, Rollins School of Public Health; Professor of Medicine, Division of Infectious Diseases, School of Medicine, Emory University

ADEL MAHMOUD, President, Merck Vaccines, Merck and Co, Inc.

LINDA MEARNS, Scientist and Deputy Director, Environmental and Societal Impacts Group, National Center for Atmospheric Research

FREDERICK MURPHY, Professor, Schools of Veterinary Medicine and Medicine, University of California, Davis

MICHAEL OSTERHOLM, Director, Center for Infectious Disease Research and Public Policy, Professor, School of Public Health, University of Minnesota

CLARENCE PETERS, Professor, Departments of Microbiology and Immunology and Pathology, University of Texas Medical Branch

PATRICIA QUINLISK, Iowa State Epidemiologist, Iowa Department of Public Health

FREDERICK SPARLING, Professor of Medicine and Microbiology and Immunology, University of North Carolina, Chapel Hill

ROBERT WEBSTER, Professor, Virology Division, Department of Infectious Diseases, Rose Marie Thomas Chair, St. Jude Children's Research Hospital, Memphis, TN

MARK WILSON, Associate Professor of Epidemiology, Associate Chair, Ecology and Evolutionary Biology, University of Michigan
MARY WILSON, Associate Professor of Medicine, Harvard Medical School, Associate Professor of Population and International Health, Harvard School of Public Health

Staff

MARK S. SMOLINSKI, Study Director
PATRICIA A. CUFF, Research Associate
KATHERINE A. OBERHOLTZER, Project Assistant
RICHARD MILLER, Director, Medical Follow-up Agency

REVIEWERS

The preface has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council and the Institute of Medicine. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Samuel L. Katz, Duke University, Durham, North Carolina
Farzad Mostashari, New York City Department of Health and Mental Hygiene, New York, New York
Robert G. Webster, St. Jude Children's Research Hospital, Memphis, Tennessee

Although the reviewers listed above have provided constructive comments and suggestions, they were not asked to endorse the final draft of the preface before its release. The review of this report was overseen by the Institute of Medicine. Responsibility for the final content of this preface rests entirely with the authors.