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high morbidity and mortality among those who cannot—grow in the absence of an equity plan to deliver the tools to those most at risk. Preventing such a future is among the most important goals of global health. ■ ■FURTHER READING Bukhman G et al: The Lancet NCDI Poverty Commission: Bridging a gap in universal health coverage for the poorest billion. Lancet 396:991, 2020. Cancedda C et al: Strengthening health systems while responding to a health crisis: Lessons learned by a nongovernmental organization during the Ebola virus disease epidemic in Sierra Leone. J Infect Dis 214:S153, 2016. Farmer P: Chronic infectious disease and the future of health care delivery. N Engl J Med 369:2424, 2013. Farmer P: Fevers, Feuds, and Diamonds: Ebola and the Ravages of History. New York, Farrar, Straus and Giroux, 2020. GBD 2019 Diseases and Injuries Collaborators: Global Burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1204, 2020. GBD 2019 Risk Factors Collaborators: Global Burden of 87 risk factors in 204 countries and territories, 1990–2019: A system atic analysis for the Global Burden of Disease Study 2019. Lancet 396:1223, 2020. Institute for Health Metrics and Evaluation: Financing Global Health 2021: Global Health Priorities in a Time of Change. Seattle, Institute for Health Metrics and Evaluation, 2023. Kim JY et al: Redefining global health-care delivery. Lancet 382:1060, 2013. Watkins DA et al: Alma-Ata at 40 years: Reflections from the Lancet Commission on Investing in Health. Lancet 392:1434, 2018. David M. Morens, Anthony S. Fauci

Emerging and

Re-Emerging

Infectious Diseases EMERGING INFECTIOUS DISEASES: DEFINITION AND CLASSIFICATION Pathogenic microorganisms and viruses have existed in the environ ment and in numerous animal species for millions of years. Humans have presumably had endemic infectious diseases since the

origins of the human species, about 2 million years ago. However, until about 12,000 years ago, humans lived and moved about in small clans and tribal groups, experiencing limited contact with other humans or animals. During this pre-neolithic era, endemic infections were probably limited mostly to skin and gastrointestinal organisms. Even though contact with the environment and with animals undoubtedly led to sporadic infections with non-endemic pathogens, there was little opportunity for these pathogens to become widely spread among humans, i.e., to become epidemic. This situation changed dramatically in the early neolithic age, about 10,000 BCE, in association with domestication of animals for food and for labor, planting and fertilization of crops, storage of water, organized disposal or diversion of sewage, growth of large settled villages and towns, labor specialization, and an enormous increase in human crowd ing and animal–human contacts. These new elements of human societal existence were associated with the emergence and human adaptation

of existing enzootic and environmental organisms within populations large enough to sustain human-to-human spread, i.e., to cause emerging epidemics. It is believed that in this period the first significant emerging infectious diseases (EIDs) appeared. The likelihood that numerous pandemic emergences occurred between the onset of the neolithic era and the era of microbial iden tification (beginning in the nineteenth century) is suggested by the large number of human pathogens that are today found globally in genetic and phenotypic forms that are identical or highly similar to each other—e.g., skin organisms such as staphylococci (Chap. 152), streptococci (Chap. 153), pneumococci (Chap. 151), and corynebacte ria (Chap. 155); enteric pathogens like Escherichia coli (Chap. 166) and salmonellae (Chap. 171); latently infecting neural viruses like herpes viruses (Chap. 200); and sexually transmitted agents like human papil lomavirus (Chap. 203), gonorrhea (Chap. 161), and syphilis (Chap. 187). In some cases, microbial/virologic phylogenetic data allow rough estimation of the times of pathogen emergences, but even without such data, it is obvious that pandemic spread had to have occurred at some time in the past if we are to explain the global prevalence of many human pathogens today. EIDs and indeed pandemic IDs are thus a very old human phenomenon that we have only recently begun to consider.

Emerging and Re-Emerging Infectious Diseases

CHAPTER 486 EIDs have been defined and characterized as shown in Table 486-1. The importance of distinguishing between newly emerging IDs and re-emerging IDs (REIDs) has particular significance for clinicians, who usually are not only among the first to encounter the newly emerging group, but also among those with the greatest expertise in recogniz ing and dealing with the second group. It is also of note (Table 486-1) that subcategories of REIDs include accidental release of pathogens by human activities, e.g., vaccine-derived polioviruses or the sudden 1977 pandemic appearance of a long-extinct 1950s-era H1N1 influenza virus, presumably a result of undisclosed vaccine or other virologic research that led to viral “escape.” EMERGING INFECTIOUS DISEASES: THEIR IMPORTANCE EIDs have been among the leading causes of death, disability, and social disruption throughout recorded human history (Table 486-2). For example, it is believed by some historians that at least two of the biblical pharaonic plagues (around the thirteenth century BCE) were EIDs. The regionally pandemic “Plague of Athens” (430–425 BCE) is said to have brought about the end of the “Golden Age” of Greece. TABLE 486-1 Emerging and Re-Emerging Infectious Diseases: Definitions, Categories, and Examples Emerging infectious diseases (EIDs) are those recognized in humans for the first time, e.g., HIV/AIDS, Nipah virus infection, or severe acute respiratory syndrome (SARS) and COVID-19. Re-emerging infectious diseases (REIDs) are those that have infected humans in the past and continue to reappear in new locations (e.g., West Nile

virus in the United States and Russia in 1999), reappear in resistant or otherwise phenotypically different forms (e.g., influenza, methicillin-resistant Staphylococcus aureus, drug-resistant falciparum malaria), or reappear after apparent control or elimination (e.g., poliomyelitis in parts of Africa, cholera in Haiti in 2010 and elsewhere in association with natural disasters, wars, and mass migrations) or under unusual circumstances (e.g., deliberately released agents, including the 2001 anthrax bioterrorism attacks). Important subcategories of REIDs include the following: REIDs related to accidental human release—e.g., vaccine-derived polioviruses, epizootic vaccinia virus, and the 1979 Sverdlovsk laboratory explosion releasing anthrax spores REIDs caused by human intent to harm (bioterrorism)—e.g., the 1997 Oregon salad bar poisonings and the 2001 anthrax spore attacks in the United States Established infectious diseases or endemic infectious diseases are those that have been prevalent for a sufficient period of time to allow for a relatively stable and predictable level of morbidity and mortality (e.g., many viral and bacterial respiratory and diarrheal diseases, including respiratory syncytial virus, endemic coronaviruses, noroviruses, pneumococcal disease, drug-susceptible malaria and tuberculosis, and many other tropical diseases such as helminthic and other parasitic diseases, many nosocomial infections).

TABLE 486-2 Selected Emerging Infectious Diseases of Note, 430 BCE to 2024 AD YEAR NAME DEATHS COMMENTS 430 BCE “Plague of Athens” ~100,000 First identified transregional pandemic

Justinian plague (Yersinia pestis) 30–50 million Pandemic; killed half of then-known world population 1340s “Black Death” (Yersinia pestis) ~50 million Pandemic; killed at least one-quarter of the known world population

Syphilis (Treponema pallidum)

> 50,000 Pandemic brought to Europe from the Americas c. 1500 Tuberculosis High millions Ancient disease; became pandemic in Middle Ages

Hueyzahuatl (Variola major) 3.5 million Pandemic brought to New World by Europeans 1793–1798 “The American plague” ~25,000 Yellow fever terrorized colonial America

Second cholera pandemic (Paris) 18,402 Spread from India to Europe/Western Hemisphere PART 17 Global Medicine

“Spanish” influenza ~50 million Led to additional pandemics in 1957, 1968, 2009 1976–2020 Ebola More than 15,000 deaths First recognized in 1976; 29 regional epidemics to 2020

Acute hemorrhagic conjunctivitis Rare deaths First recognized in 1969; pandemic in 1981

HIV/AIDS

> 40 million First recognized in 1981; ongoing pandemic

SARS

Near-pandemic

H1N1 “swine flu” 284,000 Fifth influenza pandemic in less than 100 years

Chikungunya Uncommon but high morbidity Pandemic, mosquito-borne

Zika ~1000?* Pandemic, mosquito-borne *Zika mortality has not been fully established. Most deaths are fetal or related to outcomes of severe congenital infections. Source: Reproduced with permission from DM Morens, AS Fauci: Emerging pandemic diseases: How we got to COVID-19. Cell 182:1077, 2020. Both the Justinian plague (544 AD) and the Black Death pandemics of bubonic/pneumonic plague of 1347–1349 AD (Chap. 176) depopu lated large segments of Europe and surrounding regions. The cholera (Chap. 173) pandemic of 1831–1832 killed large numbers of Europeans and ushered in the first modern studies to characterize disease and death in modern epidemiologic terms. The past century has featured three of the most highly fatal pan demics the world has ever experienced: the 1918 H1N1 influenza (Chap. 206) pandemic, thought to have been the deadliest pandemic in human history; the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) pandemic (Chap. 208), which so far has killed more than 40 million people; and the COVID-19 pandemic (Chap. 205), which is now (2024) in its fifth year, having killed more than 7 million people so far, and by some estimates as West Nile virus Ebola virus Cryptosporidiosis Enterovirus D68 Heartland virus Powassan virus Antimicrobialresistant threats

- CRE
- C. difficile
- MRSA - N. gonorrhoeae H3N2v influenza Cyclosporiasis E. coli O157:H7 Hepatitis C vCJD Lyme disease Measles Listeriosis Adenovirus 14 Human mpox Acute flaccid myelitis Bourbon virus 2009 H1N1 influenza Anthrax bioterrorism Hantavirus pulmonary syndrome Dengue Chikungunya Zika virus Yellow fever Human African trypanosomiasis Cholera Plague February 2020 Newly emerging Re-emerging/resurging “Deliberately emerging” FIGURE 486-1 Selected newly emerging, re-emerging, and human-caused emergences over recent decades. (Reproduced with permission from DM Morens, AS Fauci: Emerging pandemic diseases: How we got to COVID-19. Cell 182:1077, 2020.)

many as 20 million. In addition to the highly fatal and the potentially fatal pandemics of the past century, recent decades featured a seeming Pandora’s box of EIDS (Fig. 486-1), including novel pathogenic agents, re-emerging agents, and agents that are known but have re-emerged in entirely new forms, e.g., dengue hemorrhagic fever (Chap. 215), Zika, and numerous antibiotic-resistant bacteria (Chap. 150). It appears that we have entered a new era in which emergences and re-emergences of IDs are increasing in frequency and impact. RESPONSE OF THE MEDICAL COMMUNITY TO INFECTIOUS DISEASES Acceptance of the concept of infection—almost complete before 1890—quickly led to treatments such as antitoxins and immune plasmas, soon thereafter to non-vaccinia immunogens, by the 1930s to powerful Diphtheria Drug-resistant malaria Akhmeta virus MERS-CoV E. coli O104:H4 Rift Valley fever Typhoid fever SFTSV bunyavirus E. coli O157:H7 PNA syndrome H5N6 influenza Coronavirus disease 2019 (COVID-19) H10N8 influenza H7N9

influenza Lassa fever HIV H5N1 influenza SARS Nipah virus Hendra virus Nipah virus Enterovirus 71 Human mpox Ebola virus Zika virus Marburg virus MDR/XDR tuberculosis

antibiotics, and, by the 1950s, to antivirals. Ironically, however, these successes, which many considered miraculous, also led to significant overconfidence. By the 1960s, experts were predicting that infectious diseases would be conquered. In 1981 the U.S. Centers for Disease Control and Prevention was reorganized to pivot away from IDs and toward chronic and lifestyle-associated diseases that caused the great est U.S. mortality and years of productive life lost (YPLL). Then, before the year was out, the world was shocked by the appearance of the AIDS pandemic, caused by a previously unknown body fluid–transmitted virus: HIV. Although the AIDS pandemic was an enormous challenge, the biomedical research community, together with the pharmaceutical industry, eventually responded, most importantly by developing effec tive combination antiretroviral therapies, as well as risk-reduction pro grams such as needle exchanges and education in safe sexual practices. A 1992 report of the Institute of Medicine (IOM; now the National Academy of Medicine) drew attention to the enormous problem of emerging infections, coined the term and characterized the scope of EIDs, defined the variables associated with emergences, and made farreaching recommendations for preparedness, response, research, train ing, and medical and public health practice. Today, clinicians, scientists, public health officials, and government leaders work together within a global infrastructure of EID awareness, in which preparedness and response capacity have been increasingly successful. Such successes include stopping SARS from becoming globally pandemic and then eradicating its virus as a human pathogen; turning AIDS from an inevitably fatal disease to one associated with a normal lifespan for most patients who take antiviral medication; establishing the United States President’s Emergency Plan for AIDS Relief (PEPFAR) program to bring life-saving AIDS treatment to the poorest corners of the world; and success in controlling the 2014–2016 regional Ebola (Chap. 216) pandemic in West Africa, without a vaccine or proven treatment, using standard public health measures alone. This modern global EID control infrastructure includes not only vigorous detection of and response to EIDs, including international health regulations and EID oversight by the World Health Organiza tion (WHO), but also controlling and even eradicating existing dis eases. Apart from SARS, mentioned above, in 1980 smallpox (Chap. 201) was declared eradicated, a feat considered by some to be the most sig nificant accomplishment in medical history, given the millions killed by the virus over many thousands of years. In 2011, the veterinary disease rinderpest was declared eradicated as well. A number of other important IDs now appear to be either close to eradication—e.g., polio myelitis (Chap. 210), dracunculiasis (Chap. 240)—or significantly controlled globally with eradication at least on the horizon—e.g., mea sles (Chap. 211), rubella (Chap. 212), yaws (Chap. 183). All aspects of ID control, including controlling and trying to eradicate old emerging and still-re-emerging IDs, as well as preventing and controlling the emergences of new ones, work toward the same goal of reducing the impact of IDs on global human morbidity and mortality.
MECHANISMS OF EMERGENCE Pathogens that newly emerge into humans are acquired via several dif ferent mechanisms. Some emerging pathogens are dead-end infections, i.e., they are not usually transmitted onward to other humans, and thus are not likely to become epidemic. Common examples of such infec tions are those arising from environmental “point-source exposures,” in which many humans are exposed to a pathogen in one place over a very narrow window of time, e.g., coccidioidomycosis (Chap. 219) and histoplasmosis (Chap. 218) outbreaks associated with excavations, norovirus (Chap. 209) outbreaks aboard cruise ships (due to sewagecontaminated water), or bacterial/bacterial toxin contamination of foods in restaurants or at picnic or banquet

events. Such point-source emergences tend to be sporadic, unpredictable, and of very short dura tion, the causative organisms being from the environment and usually well known and easily diagnosed, e.g., norovirus outbreaks identified by epidemiologic and clinical characteristics, or easily tested for, e.g., bacterial culture of enteric pathogens. They are typically short out breaks of high morbidity but low mortality.

A second category of disease emergence, animal-to-human host switching, is of relevance to both newly emerging and re-emerging dis eases and accounts for virtually all novel pandemics (e.g., the influenza pandemic of 1918, HIV/AIDS) and many re-emerging IDs as well (e.g., human mpox, human Rift Valley fever). In the past two decades there has been much theoretical and microbiologic and virologic research on how such zoonotic emergences occur. Current concepts are briefly summarized. Most animal and human pathogens, and especially viruses infecting mammals, are specifically adapted to a narrow host group, such as a single host species—e.g., the many New World hanta viruses, which tend to have been finely adapted to single rodent species over thousands of years. Such pathogens may have a limited ability to infect closely related species, and they are not normally highly trans missible between members of new host species they do infect. Measles, for example, is a human-adapted virus which can infect some primate species, but despite its extraordinary contagiousness for humans, it is not naturally transmitted between primates. How then do pathogen emergences into new host species, and most importantly into humans, occur? Emerging and Re-Emerging Infectious Diseases
CHAPTER 486 This is an extraordinarily difficult question to answer, since emer gences tend to occur in a “black box,” out of sight of scientists and epi demiologists, and indeed typically in remote locales. But it is theorized that such emergences result from uncommon constellations of other wise low-risk molecular genomic and ecologic events (Chaps. 125 and 126), which include pathogens (particularly viruses) with high mutation rates, such as many RNA viruses; intense or unusual human–animal contact; and chance. A theoretical model (Fig. 486-2) posits that a virus well adapted to its primary host is likely to be non-adapted or at least far less adapted to other potential hosts, even closely related ones. But since viruses have high mutation rates, there will always be some virions that have mutated to become less well adapted to their own hosts and, by chance, some of these may “accidentally” have acquired an ability to adapt to a new host. Presumably, very few of these mutated viruses come into contact with potential new hosts before they are “purged,” but if one or more virions is (1) is not significantly de-adapted to its normal host, (2) is, at the same time, capable of adapting to a new host, and (3) is able to cross a “fitness valley” of de-adaptation to the old host and neo-adaptation to the new host, a host switch may occur (Fig. 486-2). This model attempts to explain why major emergences are relatively uncommon (e.g., despite countless billions of viral muta tions occurring daily, looking back over the past 500 years, there has only been about one new recognized influenza pandemic every 30 or so years). It might be said, teleologically, that pathogens are constantly “trying” to emerge, but almost always failing to do so. A third category of disease emergence relates to mutations that occur in pathogens that are already human adapted, the best-known example being development of antibiotic resistance in a bacterial species previously susceptible to particular antibiotics. Although antibiotic-resistant pathogens live in the soil and other natural envi ronments and have done so since before human-developed antibiotics existed, bacteria are also capable of horizontally transmitting to other bacteria DNA-containing resistance genes, and these may be selected for in Darwinian fashion, e.g., by medical and hospital environments in which antibiotics are administered (Chap. 147). An analogous prin ciple even applies to viruses. Particularly as viruses gain access to

larger human populations via crowding and human movement, mutation may lead to a fitness advantage, e.g., to a more transmissible phenotype that may escape natural and vaccine-induced immunity, and may even be associated with increased pathogenicity, as may have happened with the SARS-CoV-2 delta variant in 2022. A similar phenomenon was seen beginning in 2014 with the re-emergence of enterovirus D68 (EV-D68) to cause global epidemics of acute flaccid myelitis.
VARIABLES ASSOCIATED WITH

DISEASE EMERGENCE Whatever the mechanisms of pathogen emergence may be, it has become clear that the determinants of emergence—i.e., variables that provide opportunities for pathogens in disturbed ecosystems to emerge, typically beginning with the host switch of an animal pathogen

Steep Fitness Valley Shallow Fitness Valley Fitness Fitness Donor Species Recipient Species Donor Species Recipient Species PART 17 Global Medicine Mutation frequency Mutation frequency A B Chance Transmission of Multiple Advantageous Mutations Progressive Adaptation in the Recipient Species Donor Species Recipient Species C D FIGURE 486-2 A theoretical model of how animal-to-human pathogen host-switching might occur, in this case the pathogen being a virus. The light-colored viruses represent those adapted to the transmitting host, and the darkcolored viruses represent those mutating in the direction of the host to which the virus is adapting. A and B compare two different situations in which there is a deep virus–host fitness valley (A) or a shallow fitness valley (B), the valleys representing the degree of challenges that mutable viruses need to overcome to be able to infect new host species. To be able to cross the steep fitness valley, a virus that is at peak adaptation to host 1 must mutate significantly in the direction of de-adaptation to be able to infect host 2, an event that is more likely if the virus has a high natural rate of mutations. In B, a narrow fitness valley is more easily crossed, resulting in a host switch. The phylogenetic trees in C and D show the adaptational mutations that necessarily occur for a virus that has crossed a steep fitness valley (shown in A) as it adapts to the new host (C). In D, a virus that has crossed a narrow fitness valley (as shown in B) does not “need to” adapt to the new host as significantly (C) to be able to initiate and sustain transmission between hosts of the new species. (Reproduced with permission from DM Morens, AS Fauci: Emerging pandemic diseases: How we got to COVID-19. Cell 182:1077, 2020.) within a geographically identified global “hot spot”—are largely related to humans and human activities (Fig. 486-3). Most of the important variables associated with pathogen emergence are either activities of the human host—demographics and behavior including crowding, human movement, sexual practices, and occupation (Fig. 486-3, upper right)—or variables that reflect human degradation of the environment— poverty and social ills, wars, displacements, land use practices, and inadequate public health infrastructure (Fig. 486-3, lower right). Even though HIV clades probably emerged separately and independently more than a century ago, AIDS did not become pandemic until signifi cant viral transmission could be sustained within a modern humandominated global environment, once composed of remote villages but more recently replaced by urban environments, transnational travel and commercial sex work, meeting places for men who have sex with men, IV drug use, and blood product transfusions. The emergence of hyperendemic dengue and dengue hemorrhagic fever after World War II was associated with urban crowding and domestic water storage. The United States epidemic of hepatitis C (Chaps. 350 and 352), which began in the 1960s, was associated with blood product transfusions and injection drug use. The emergence of hantavirus pulmonary syn drome was associated with construction of human-made peridomestic outbuildings and unfinished basements that housed infected reservoir

rodents during the winter. The emergence of Nipah virus (Chap. 204) in Malaysia in 1998 was associated with both deforesta tion and intensive pig farming practices. The 2003 United States mpox outbreak was associated with unregulated importation of rodent pets from enzootic areas. Emer gence in China of both H5N1 and H7N9 poultry influenza A (“bird flu”) was associ ated with crowded live animal markets, and it stopped quickly when these markets were shut down. The 2010 cholera epidemic in Haiti followed a devastating earthquake associated with human displacement, loss of access to safe water, inadequate medi cal and social support, and the arrival of aid from foreign locales that inadvertently imported cholera organisms. It should be noted that emergence vari ables are not always identical between the newly emerging and re-emerging IDs. Reemergences of known pathogens are more likely to result from societal failures to cre ate and sustain safe human environments, and to disruption of balanced ecosystems in the natural world. Emergences of new pathogens such as pandemic influenza, on the other hand, are sometimes unique and highly improbable events. It is noteworthy that for diseases like influenza, in which transmission is facilitated by crowding and human movement, the intervals between pandemics are about the same today as they were 500 years ago, despite an eightfold increase in the global population and the advent of modern rapid global travel. This suggests that influenza pandemics are rare stochastic events unrelated to the size of the population that spreads them, even though population growth spreads them more widely and more quickly than they once did. EXAMPLES OF CHALLENGES OF DISEASE EMERGENCE AND HOW THEY ARE BEING MET The complexities of potential control of pathogen emergence and re-mergence are noteworthy: each emergent disease presents a differ ent challenge, as briefly summarized below for three selected patho gens of global importance. ■ ■INFLUENZA A The reservoir of influenza A viruses is the global pool of wild waterfowl and shorebirds. All human, other mammalian, and poultry-associated influenza viruses are derived from this pool. The 1918 pandemic influenza H1N1 “founder” virus either was derived directly from a waterfowl or had a brief period in another mammalian host before becoming pandemic. Humans immediately transmitted it to domestic pigs in 1918; descendants of those human and pig viruses still exist in whole or in part, having devolved into separate and increasingly diver gent lineages over the past century. The three influenza pandemics that have occurred since 1918 were all caused by genetic descendants of the 1918 virus, having been naturally modified by genetic changes of sev eral types. Such mutations make control and prevention difficult. The viruses have multiple mutational mechanisms to circumvent human immunity, including (1) genetic “drift” (point mutations); (2) “shift” (importation of different avian hemagglutinins with or without impor tation of neuraminidases); (3) intrasubtype reassortments (importation

• Cell tropism • Alternative and co-receptors • ADE and related phenomena • Genetic/inherent susceptibility • Immune protection • Genetic diversity • Genetic evolution and change • Variable infectivity • Immunodominant antigens • Co-pathogenesis ENVIRONMENT AGENT FIGURE 486-3 Infectious agents, hosts, and the environment: determinants of disease emergence, re-emergence and persistence. Factors most closely associated with re-emergences are highlighted, including accidental and purposeful human release of infectious pathogens. (Reproduced with permission from DM Morens, AS Fauci: Emerging pandemic diseases: How we got to COVID-19. Cell 182:1077, 2020.) of whole human hemagglutinin or neuraminidase subtype variants), and (4) glycosylation of external protein sites that can alter viral struc ture and function. With a broad repertoire of mutational possibilities, a human-adapted virus may repeatedly escape population immunity elicited by natural infection and vaccination, as has been the case with the 1968 pandemic H3N2 virus, which is still causing infections and death, and escaping vaccine immunity, 56 years after its

appearance. During this interval it has also periodically, and for unknown reasons, increased in pathogenicity. Influenza control is further confounded by the fact that influenza A is a nonsystemic virus that replicates on a one-cell-deep layer of respiratory epithelium, without fully encountering the human systemic immune system. Because influenza has a very short incubation period, there is too little time for the virus to fully elicit memory immune cells, the virus only encountering the less specific innate immune system, as well as IgA and IgM antibodies secreted across the epithelium from the systemic circulation (only fully effective in high concentration). It also has an advantage in replicating only in an immune environ ment of the upper respiratory tract that tolerates multiple continuous antigenic exposures, including brief viral infections, without massive immune responses that could be harmful to the host. Thus, influenza vaccines are at best incompletely effective and protect for only a matter of months. This will be an important challenge in attempts to develop universal influenza vaccines. It is also noteworthy that pandemic and postpandemic influenza viruses are increasingly better adapted to the modern world. Before 1889, the predominant travel mechanism of influenza spread was by coach, globalization of spread taking as much as a year or more, or failing to occur at all. Until the 1700s, the Americas and Europe did not even appear to have been on the same influenza pandemic cycles. (Although the earliest genetically sequenced influenza viruses date to 1918, scholars have for several centuries presumptively identified influenza pandemics on the basis of characteristic clinical-pathologic signs and symptoms, epidemiologic patterns, and route and rapid ity of global spread). In the 1889 pandemic, presumed influenza was spread from East Asia to Europe by rail. The 1918 and 1957 pandemics were spread predominantly by ship, and the 1968 and 2009 pandem ics predominantly by air. Influenza spread is ideally suited to human movement and crowding. Furthermore, high rates of presymptomatic and subsymptomatic infection allow the virus to be transmitted by

• Demographics and behavior – International travel/trade/recreational – Sex – Occupation – Antibiotic misuse HOST Emerging and Re-Emerging Infectious Diseases
CHAPTER 486 • Animal exposures • Environmental degradation • Climate and weather • Economic development/land use • Technology/industry/agriculture • Poverty and social ills • Wars, famines, natural disasters • Lack of public health infrastructure • Lack of political will DISEASE persons who do not know they are infectious or capable of transmitting, thwarting attempts to lower transmission by public health measures. In short, influenza A is an avian virus emerging out of nature. It remains difficult to prevent or to identify in advance an avian influ enza virus with pandemic potential. At this point we have limited ability to control constantly mutating viruses once they have become human-adapted. ■ ■SARS AND SARS-CoV2 The sarbecoviruses (SARS-like beta-coronaviruses) are similar to influenza in some respects and different in others. Their natural reser voir is not birds but bats, and the main human host receptor for viral infection is the angiotensin-converting enzyme 2 (ACE2) receptor, as opposed to respiratory tract sialic acid receptors for influenza. Because ACE2 receptors on bats, many other mammals, and humans are quite similar, sarbecoviruses can be thought of as potentially preadapted to humans. It is in part for this reason that many experts predict future emergences of these viruses. Similar to influenza, SARS-CoV2 is a respiratory virus that does not produce true viremia, has a short incubation period and incomplete exposure to the systemic immune system, and often causes asymptom atic or subsymptomatic infection, bedeviling control with public health measures such as social distancing and isolation. Also similar to influ enza, and despite its moderate transmissibility, it can be “superspread” in crowded environments such as restaurants and bars, churches, sports venues, or any crowded place, especially if there is imperfect airflow and humidity. In addition, like influenza,

SARS-CoV2 evolves continually (not however by genetic reassortment, but by mutation and recombination), continually escapes population immunity, and is imperfectly prevented by vaccines. As has been the case with influenza, control of emerging SARS-CoV2, and prevention of population spread and large-scale mortality, remains difficult. ■ ■DENGUE A third example of the complexities of emergence and response, in this case re-emergence, is dengue. An Aedes aegypti–borne flavivirus, “dengue virus” is actually four closely related viruses (DEN-1, DEN-2, DEN-3, and DEN-4) that interact with each other serologically and with respect to immunity and pathogenicity. Dengue is believed to have emerged more than 400 years ago, perhaps much earlier, and has

3858 been endemic and hyperendemic around the tropical belt ever since, re-emerging sporadically to cause high morbidity and sometimes high mortality. Emergences now occur repeatedly in the U.S. commonwealths of the Northern Mariana Islands and Puerto Rico, in the U.S. territories of Guam, American Samoa, and the United States Virgin Islands, and in the United States–affiliated Federated States of Micronesia. At one time, large-scale dengue epidemics were common in the continental United States, e.g., a major epidemic in Philadelphia in 1780; in recent years smaller outbreaks have occurred in southern states. Despite the fact that all dengue cases occur within a human-to-mosquito-to-human transmission cycle, without direct human-to-human transmission, den gue re-emergences can be so explosive that they mimic the most highly contagious respiratory viruses. During simultaneous 1977 outbreaks of dengue and influenza in Puerto Rico, within-household studies showed greater case-clustering of dengue than of influenza. PART 17 Global Medicine Dengue is highly associated with peridomestic water storage (where vector mosquitoes oviposit), lack of sanitation, crowding, and lack of screens and air conditioning. It would seem a simple matter to control dengue by controlling water storage, but even Singapore—a developed country whose residences have screens, air conditioning, excellent sanitation, and public health mosquito police who constantly patrol residences and public places to examine for breeding sites, assessing fines for even minor breeding site violations—is unable to prevent dengue outbreaks from occurring. A difficult problem seems to be that mosquitoes can oviposit in the tiniest and most inconspicuous bits of water, e.g., the slight (several millimeter) indentations in the bases of porcelain toilets where they are bolted to the floor. Although dengue was historically considered a nuisance disease, shortly after World War II (during which only 4 of more than 90,000 dengue-infected servicemen/service women died) a new and highly fatal clinical form emerged in Southeast Asia and quickly became a significant killer of children. Studied by teams of Thai and American scientists, the new clinical form was classified as dengue hemorrhagic fever (DHF) and, in its most severe form, dengue shock syndrome (DSS), a result of sudden massive extravasation of intravascular fluids into the tissues. But the very same viruses that caused the mild form of dengue were also those that caused DHF and DSS, a puzzle that was unraveled by Halstead and others when it was learned that it was predominantly only with the second of four potential dengue infec tions (one with each of the four serotypes) that DHF/DSS occurred. Epidemiologic data were consistent with the belief that cross-reactive antibodies elicited by the first dengue infection, unable to neutralize the second virus, actually potentiate viral entry into cells via antibodydependent enhancement for the acute clinician, dealing with EIDS depends upon ecologic perspectives on infectious disease occurrence. Only in recent years have science and medicine begun to make an impact on severe dengue disease, including training of clinicians and parents, the widespread availability of oral rehydration solutions that reverse shock syndrome, and several recently developed vaccines. But fear remains that vaccines might potentiate more

severe disease, and dengue remains among the greatest re-emerging disease problems for more than 3 billion people. The three emerging disease examples noted above exemplify the complexity of disease emergence: the role of demographic and envi ronmental variables (live poultry markets in severe human influenza; human-made peridomestic environments in dengue), pathogen inter actions (partial immune crosses in influenza and dengue, related to both protection and disease severity, as well as to diagnostic dif ficulties), complete or partial immune escape (all three pathogens), immunopathogenesis (1918 influenza and dengue), inherent problems in vaccine prevention (all three diseases), animal reservoir hosts of progenitor viruses (all three diseases), viral evolution via mutations (all three diseases), and many other factors. THE ROLE OF CLINICIANS AND LABORATORIANS IN EID CONTROL Clinicians and laboratorians are on the front lines of EID control and response efforts, and they must continue to play a leading role in global pandemic preparedness and response. It is typically the astute

clinician who first recognizes a new disease, usually because signs and symptoms, or complications, are not typical of similar diseases. For example, in the 1918 influenza pandemic there was never-before-seen pneumonia-associated case-fatality featuring viral infection and bacterial co-pathogenesis, the bacteria being normal oral flora and the pneumonia producing an anatomic pattern, diagnosed clinically or in some cases by x-ray, which was invariably bronchopneumonic. In the 1950s, emergence of dengue hemorrhagic fever was associated with never-before-seen complications, including shock and death, occurring in association with endemic dengue viruses and in epidemiologic patterns that were novel (shock occurring only in infants under one, and in older toddlers and school-aged children, but sparing children between these ages, as well as those in and beyond the older teenage years). In fact, it was the bizarre and unprecedented age-specific mortality patterns of DSS that suggested its pathogenetic mechanisms. That legionellosis (Chap. 164), first identi fied in 1976, must have been an unknown emerging disease was learned when clinicians were unable to make a pathogen-specific pneumonia diagnosis and laboratories were unable to isolate a pathogen. A similar profile was seen with SARS, emerging in 2002–2003, when adults with respiratory/constitutional symptoms typical of many respiratory viruses experienced an approximate 10% case-fatality rate. It is not only primary care providers who are in a position to recognize newly emerging diseases. Both emerging acute hemorrhagic conjuncti vitis (AHC) in 1969–1970 and emerging human Rift Valley fever (RVF) in 1977 were largely identified by ophthalmologists who observed the unexpected: severe and explosively epidemic conjunctivitis with AHC, and blindness associated with macular infiltrates in RVF. In 1981, it was pathologists who identified Pneumocystis carinii (now jirovecii) pneumonia in autopsies of previously healthy young men, joining epi demiologists and clinicians in characterizing a new clinical-pathologic syndrome that was eventually recognized as AIDS. And it was pediatric neurologists who played a major role in identifying emergent enterovirus D68–associated acute flaccid myelitis beginning in about 2014. Even looking back in history to a time before the microbial era, we can identify the same phenomenon: it was a “proto-epidemiologist” who first imag ined that cervical cancer was the result of a contagious disease when he showed, in the 1840s, that nuns never suffered from it. Among the skills of medical practitioners related to a key front-line role in dealing with EIDs are the following: (1) abiding curiosity; (2) the ability to sense something out of the ordinary and pursue suspicions, using the medical history, physical examination, and laboratory tests (Chaps. 8 and 505); (3) a sense of the epidemiology of different diseases that allows imagination of how an illness might have been acquired, of the mechanism of acquisition—environmental, respiratory, inocula tion (including sexual inoculation), gastrointestinal, occupational, etc. (Fig. 486-3); (4) whether there are family or other case clusters, and whether

such clusters represent common-source exposure, zoonotic exposure, or person-to-person transmission; (5) determination of an approximate incubation period and duration of infectivity; (6) a close relationship with the diagnostic laboratory and knowledge of when to seek additional laboratory follow-up; (7) a close relationship with allied practitioners, including specialists, and with disease researchers; (8) a close relationship with public health workers, diligence in promptly reporting reportable diseases and reportable disease syndromes, and awareness of outbreaks that may be occurring in the community; (9) regular reading of the medical literature to stay grounded within and outside of one’s specialty; and (10) skill at communicating with and eliciting trust from patients, which appears to maximize the chance of finding clues that may be easily missed. History tells us that EIDs will certainly continue to appear, includ ing some so novel that they cannot even be imagined. An important component of the biomedical and public health enterprise is the ability to recognize, diagnose, and begin to control EIDs at the earliest pos sible time, and to limit their spread so that emergences do not evolve into epidemics. This requires coordinated efforts of those in multiple disciplines, communicating with each other rapidly and effectively. It is a part of the significant responsibilities of medical, biomedical, and public health practitioners, who together have the critical skill sets needed to confront the existential threats of EIDs.

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