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14 Emerging and Reemerging Infectious Disease Threats

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Throughout history, infectious diseases have been inextricably linked with human health, affecting the development and advancement of societies as well as human evolution.[1,2] Those linkages remain well defined today, as infectious pathogens find new ways to exploit human vulnerabilities and elude control efforts across a highly connected world. Widespread movement of people, animals, and goods, exploding population numbers, urban development, environmental degradation, centralized food production, and other contributing factors (Table 14-1) have given microbes rapid and easy access to new populations and geographic areas and spawned a host of emerging and reemerging infectious diseases—the majority of which are zoonotic (Table 14-2).[3] With their remarkable adaptability, emerging infections can spread quickly and gain strongholds to become endemic diseases, as most profoundly demonstrated by the decades-long pandemic of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS).

Data from the Global Burden of Disease Study 2010 (GBD 2010), a landmark collaboration of 486 scientists from 302 institutions across 50 countries,[4] indicate that nearly one fourth of the estimated 52.8 million deaths that occurred in 2010 were associated with infectious diseases.[5] From 1990 to 2010, overall deaths from communicable diseases declined, with significant decreases in mortality from lower respiratory tract infections (from 3.4 to 2.8 million) and diarrheal diseases (from 2.5 to 1.4 million).[5] However, infectious diseases remained leading killers, especially among young children (Fig. 14-1) and accounted for large burdens of disability-adjusted life years worldwide.[5,6] Although deaths from HIV infection/AIDS peaked in 2006 and have since showed steady declines owing to fewer new infections and increased availability of antiretroviral therapy and care, HIV infection/AIDS remains a leading cause of disease burden and death—responsible for an estimated 1.5 million deaths in 2010.[5] Tuberculosis and malaria also continue to exact a tremendous toll, each causing approximately 1.2 million deaths in 2010.[5] The multifactorial impact of infectious diseases is most prominent in low-income countries, with infectious diseases causing severe morbidity, impeding economic development, and compromising political stability.

Beyond infectious diseases, microbial agents have been identified as the cause or contributing factor in a number of chronic diseases (Table 14-3). In 2008, approximately 2 million new cancer cases were linked to infections.[7] Among the leading causes of cancer-related deaths, three are caused by infectious agents: hepatocellular carcinoma by hepatitis B and C viruses, cervical cancer by human papillomavirus, and gastric cancer by *Helicobacter pylori* bacteria. Many other potential infectious/chronic disease linkages are also being explored, including *Chlamydia pneumoniae* and multiple sclerosis,[8,9] Alzheimer's disease,[9] and atherosclerosis[10]; enteroviruses and type 1 diabetes[11,12]; and rhinoviruses and childhood asthma.[13] In addition, several genetic factors have been shown to influence infectious disease susceptibility and disease progression (Table 14-4) and hundreds of others are under investigation.[14]

The past few decades have provided numerous examples of the ongoing threat of infectious diseases and the ability of microbes to evolve, adapt, and survive. In particular, acute respiratory viruses are often among the most recognized emerging and reemerging infectious diseases because of the high disease burden they produce. Examples in the past decade include a novel coronavirus that resulted in the 2003 global outbreak of severe acute respiratory syndrome (SARS),[15] pandemic influenza A (H1N1) in 2009[16]; a newly recognized coronavirus causing severe disease in 2012 (Middle Eastern respiratory syndrome coronavirus [MERS-CoV])[17]; and avian influenza A H7N9 in China in 2013.[18] Emerging and reemerging vector-borne infections also remain priorities, as mosquito-borne viruses such as dengue and chikungunya continue to appear in new areas and tick-borne diseases continue their steady rise. In addition, increased attention is being given to environmental fungi as a cause of human and animal infections. Recent examples include the emergence of *Cryptococcus gattii* infections in the U.S. Pacific Northwest,[19,20] increasing numbers of *Coccidioides* infections, which are a major cause of community-acquired pneumonia in California and the southwest United States,[21] and novel fungal infections as a cause of health care–associated infections (HAIs).[22]

International trade and travel along with globally mobile populations present particular challenges for controlling infectious diseases, highlighting concerns for spread of known infections such as tuberculosis[23] and vaccine-preventable diseases[24] along with introduction of new threats.[25] In 2011, international tourist arrivals approached 1 billion worldwide, and they are expected to nearly double over the coming decades (Fig. 14-2).[26] Moreover, today's globalized food supply has resulted in an increasing number of foodborne illnesses, many of which have severe consequences—especially for more vulnerable populations such as children, immunocompromised individuals, and the elderly. Also on a global level is the growing problem of resistance to antimicrobial agents, which continues to impede treatment and control efforts for an increasing number of pathogens.

REEMERGING VACCINE-PREVENTABLE DISEASES

The development of safe, effective vaccines coupled with large-scale immunization programs represents the ultimate solution to infectious diseases.[27] Routine childhood immunization in the United States prevents approximately 20 million illnesses and 42,000 premature deaths, while saving nearly $70 billion in direct and societal costs for each birth cohort vaccinated.[28] Although vaccination led to the eradication of smallpox in 1980 and has brought the world closer than ever to eradication of poliomyelitis, vaccine-preventable diseases can reemerge even in the setting of high-functioning immunization programs. A variety of factors contribute to outbreaks of vaccine-preventable diseases in the vaccination era (Table 14-5).[29-32] Recently, countries in the Americas and Europe have confronted the reemergence of measles, mumps, and pertussis owing to diverse underlying causes.[33-35]

Most resurgences of vaccine-preventable diseases stem from low immunization coverage. In many parts of the world, weak primary health care systems and limited access to the most vulnerable populations result in many children being unimmunized. More recently, reduced vaccine acceptance in several affluent countries has emerged as a threat to protecting communities from vaccine-preventable diseases. Whereas in the United States less than 1% of children receive no vaccines at all,[36] some parents refuse one or more vaccines or decide to delay or increase intervals between vaccinations.

Measles

Two doses of measles-containing vaccines provide 95% vaccine efficacy, but at least 94% of the population must be vaccinated to ensure herd immunity, or population protection. Infants too young to be immunized and people who are immune compromised depend on herd immunity for protection. Accumulation of susceptible people in a community can result in periodic outbreaks when measles virus is circulating.[30] Endemic transmission of measles has been interrupted in the United States since 2000,[37] but travelers to areas where the virus still circulates account for 50 to 100 importations to the United States most years. Aggressive public health investigation of each suspected

KEYWORDS

acute respiratory infections; antibiotics; antimicrobial resistance; avian influenza; *Campylobacter*; carbapenem-resistant Enterobacteriaceae; chikungunya; cholera; *Clostridium difficile*; coronavirus; *Cryptosporidium*; dengue; diarrheal disease; Ebola hemorrhagic fever; emerging infectious diseases; epidemiology; *Escherichia coli*; foodborne disease; gastroenteritis; H1N1; H3N2; H5N1; H7N9; health care–associated infections; Heartland virus; human bocavirus; human metapneumovirus; immunizations; infectious diseases; influenza; Marburg hemorrhagic fever; measles; MERS-CoV; methicillin-resistant *Staphylococcus aureus*; mumps; norovirus; One Health; pandemic influenza; pertussis; reemerging infectious diseases; *Salmonella*; SARS; *Shigella*; vaccine-preventable diseases; vaccines; variant influenza A; vector-borne diseases; *Vibrio cholerae*; West Nile virus; zoonotic diseases

measles case is conducted to limit spread of the virus. Recently, several measles outbreaks in the United States have been associated with transmission among people who have not been vaccinated, intentionally, due to personal beliefs. In 2011, 222 measles cases occurred in the United States, the largest number of annual cases reported since 1996.[38] The most important source of imported virus in 2011 was Europe, where large outbreaks affected multiple countries. A very large outbreak in France (where an estimated 20,000 cases occurred)[39] was linked with importations to multiple countries in the Americas.[38,40] Public health response to each outbreak is expensive.[24] Because measles is rarely seen in the United States, missed diagnosis can lead to sustained exposures particularly in health care settings (Fig. 14-3).[41]

Ensuring appropriate infection control practices and complete immunization histories or evidence of immunity among health care workers is especially important given the infectiousness of measles virus.

Although in the Americas endemic transmission of measles has been eliminated and in the Western Pacific Region reaching this target is near, measles continues to cause more than 100,000 deaths each

TABLE 14-1 Factors That Contribute to the Emergence and Reemergence of Infectious Diseases

Human demographics and behavior
Human susceptibility to infection
Technology and industry
Economic development and land use
International travel and commerce
Microbial adaptation and change
Climate and weather
Changing ecosystems
Breakdown of public health measures
Poverty and social inequality
War and famine
Lack of political will
Intent to harm

Data from Smolinski MS, Hamburg MA, Lederberg J, eds, for the Committee on Emerging Microbial Threats to Health in the 21st Century, Board on Global Health, Institute of Medicine. Microbial Threats to Health: Emergence, Detection, and Response. *Washington, DC: National Academy Press; 2003.*

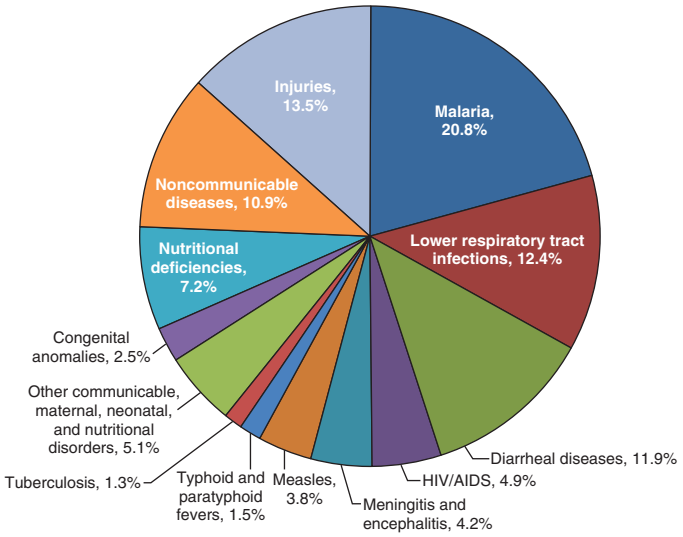

FIGURE 14-1 Causes of deaths for children 1 to 4 years of age, worldwide, 2010 (1,969,567 deaths). *(Modified from Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet. *2012;380:2095-2128.)*

TABLE 14-2 Examples of Recent Outbreaks, Pathogen Discoveries, and Other Notable Infectious Disease Events

YEAR	EVENT
2000	Outbreak of Rift Valley fever in Saudi Arabia and Yemen, representing the first reported cases of the disease outside the African continent
2003	Global outbreak of severe acute respiratory syndrome (SARS) caused by a previously unknown coronavirus associated with Chinese horseshoe bats
2003	Cases of monkeypox in the United States linked to exotic pets imported from Central Africa
2003	Reemergence of avian influenza A (H5N1) in Southeast Asia and subsequent outbreaks in Africa
2005	Marburg hemorrhagic fever outbreak in Angola
2005-2006	Large outbreak of chikungunya in the Indian Ocean islands of Réunion and Mauritius
2006	Rift Valley fever outbreak in Kenya
2007	Ebola hemorrhagic fever outbreak in the Democratic Republic of the Congo
2007	Outbreak of Nipah virus encephalitis in Bangladesh
2007	First detection in Italy of mosquito-borne transmission of chikungunya fever, previously detected only in parts of Africa and South and Southeast Asia
2007	Hemorrhagic fever outbreak in Uganda caused by a new stain of Ebola: Bundibugyo Ebola virus
2007	Outbreak of Marburg hemorrhagic fever in Uganda
2008	Ebola-Reston virus detected in pigs in the Philippines
2008	Ebola-like outbreak in Zambia due to a previously unknown virus: Lujo hemorrhagic fever virus, an arenavirus related to Lassa fever virus, which is associated with rodents
2009	Outbreak of severe fever with thrombocytopenia syndrome (SFTS) in China caused by a novel phlebovirus (the SFTS virus)
2009	Discovery of two novel tick-borne pathogens in the United States: the Heartland phlebovirus in Missouri and a pathogenic *Ehrlichia* species in Wisconsin and Minnesota
2009-2010	Influenza pandemic caused by a new influenza strain, influenza A(H1N1)
2009-2010	Locally transmitted dengue in Florida, representing the first cases acquired in the continental United States outside the Texas-Mexico border since 1945
2012	Ebola hemorrhagic fever outbreaks in Uganda and the Democratic Republic of the Congo
2012	Outbreak of Marburg hemorrhagic fever in Uganda
2011-2012	Influenza cases in the United States traced to a variant swine influenza A(H3N2) virus carried by pigs exhibited at agricultural fairs
2012	Outbreak of hantavirus pulmonary syndrome in Yosemite National Park, California
2012	A novel rhabdovirus (Bas-Congo virus) identified by whole-genome sequencing as the cause of an outbreak of acute hemorrhagic fever in the Democratic Republic of the Congo
2012-2013	Outbreak of severe respiratory disease in the Middle East caused by a novel coronavirus (MERS-CoV) that belongs to the same viral family as the SARS coronavirus
2012-2013	Influenza cases in China traced to avian influenza A(H7N9) virus in poultry

year—primarily in developing countries.[42] Enormous progress in measles immunization through supplemental immunization activities and increasing routine coverage, particularly in Africa, has led to a 74% reduction in worldwide measles deaths.[43] Despite this progress, the weak underlying immunization systems, famine, limited access associated with political disruption, and delayed emergency campaigns explain resurgences of measles in the Horn of Africa and southern Africa.[44] Low first-dose measles coverage and long intervals between campaigns offering second-dose opportunities allow rapid accumulation of children susceptible to measles and can lead to large outbreaks. Poor vaccine acceptance in selected communities, ranging from the Roma communities[45] to anthroposophists in Switzerland has led to sizable outbreaks in Europe as well.[46]

TABLE 14-3 Examples of Infectious Agents That Cause or Contribute to Chronic Diseases

PATHOGEN	CHRONIC CONDITION CAUSED/ EXACERBATED BY THIS PATHOGEN
Bacteria	
Borrelia burgdorferi	Chronic arthritis
Helicobacter pylori	Chronic gastritis and peptic ulcers
	Gastric carcinoma
	Mucosa-associated lymphoid tissue lymphoma
Viruses	
Epstein-Barr virus	Nasopharyngeal carcinoma (undifferentiated)
	Burkitt's lymphoma
	Post-transplant lymphoproliferative disease
	B-cell lymphoma
Hepatitis B and C viruses	Cirrhosis
	Hepatocellular carcinoma
Human herpesvirus 8	Kaposi sarcoma
Human immunodeficiency virus	Lymphoma
	HIV-related neurocognitive disorders and peripheral neuropathy
Human papillomavirus	Cervical carcinoma
	Anogenital and oropharyngeal cancers
Human T-lymphotropic virus type 1 (HTLV-1)	Adult T-cell leukemia/lymphoma
Parasites	
Liver flukes	Cholangiocarcinoma
Schistosoma haematobium	Bladder cancer
Prions	
Variant Creutzfeldt-Jakob disease prion	Degenerative brain disorder

TABLE 14-4 Examples of Genetic Factors That Influence Susceptibility to Disease or Disease Progression

GENETIC FACTOR	DISEASE INFLUENCE
Alleles of the chemokine receptor gene *CCR5*	Partial protection against acquisition of HIV and development of acquired immunodeficiency syndrome
Globin gene alleles (e.g., sickle globin and α- and β-thalassemias)	Partial protection against malaria
Lack of the Duffy blood group on red cells (due to a mutation in a chemokine receptor gene)	Complete protection against *Plasmodium vivax* malaria
Blood group O	Increased susceptibility to severe cholera
HLA alleles	May influence susceptibility to infection or course of disease with HIV, hepatitis B virus, measles, hantavirus pulmonary syndrome, malaria, tuberculosis, human papillomavirus infection, and coccidioidomycosis

HIV, human immunodeficiency virus; HLA, human leukocyte antigen.
Modified from Levitt AM, Khan AS, Hughes JM. Emerging and re-emerging pathogens and diseases. In: Cohen J, Powderly WG, Opal SM, eds. Infectious Diseases. *3rd ed. St. Louis: Mosby; 2010.*

TABLE 14-5 Factors That Contribute to the Reemergence of Vaccine-Preventable Diseases

FACTOR	SELECTED EXAMPLES	REFERENCES
Failure to vaccinate by health care system	Missed opportunities related to clinician practice, financial, or system constraints Weak or interrupted immunization services, as in humanitarian emergencies	29, 44
Failure to be vaccinated due to patient or parental refusal or deferral	Personal belief and religious exemptions Vaccine hesitancy	32, 33
Vaccine failure, including moderate or low vaccine efficacy and waning of immunity over time	Mumps vaccine efficacy in the setting of high force of infection Waning of immunity after acellular pertussis vaccination	34, 35
Pathogen "escape" from vaccine-induced immunity	Serotype replacement including capsular switching in *Streptococcus pneumoniae*	31

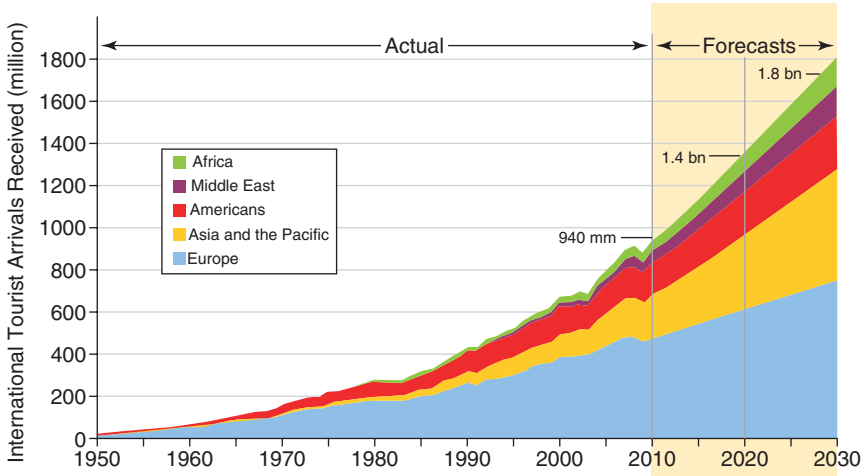

FIGURE 14-2 International tourist arrivals, actual trends and forecast, 1950-2030. *(From World Tourism Organization [UNWTO].* UNWTO Tourism Highlights*, 2012 edition. Madrid: UNWTO; 2012. Available at* http://mkt.unwto.org/en/publication/unwto-tourism-highlights-2012-edition.*)*

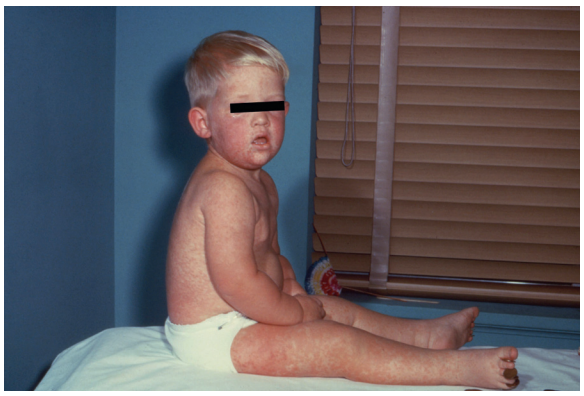

FIGURE 14-3 Measles in a child.

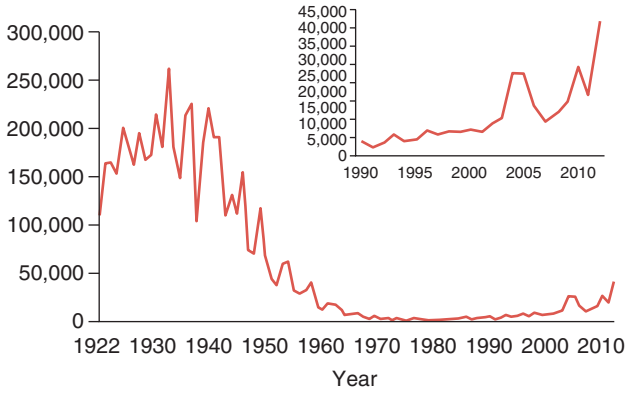

FIGURE 14-4 Cases of pertussis reported to the National Notifiable Diseases Surveillance System: 1922-2012.

Mumps

Although mumps has decreased by nearly 99% since the prevaccination era in the United States, several large outbreaks have occurred in the United States and Europe in the past decade.[34,47,48-51] Outbreak-associated disease has occurred mainly in adolescents and young adults. Despite high two-dose coverage, importation of mumps virus has been linked to outbreaks in summer camps,[52] college campuses,[47,49,53] and religious schools.[34,51] These outbreaks were difficult to control, and although the highest risk occurred among unvaccinated persons, many case-patients had received one or two doses of mumps-containing vaccine, consistent with only 80% to 85% vaccine efficacy for one- and two-dose regimens.[48,50] Although factors associated with disease include intense crowding, there is no evidence to support immune escape.[54] Recent outbreaks have been notable for very little transmission to the broader community.

Although some proponents exist, the value of administering a third dose of mumps-containing vaccine in outbreaks that occur despite high two-dose coverage has been unclear because disease tends to be decreasing by the time additional doses are provided.[55] Because most mumps outbreaks have occurred in unusual settings where there is extreme crowding or extensive personal contacts and most mumps is self-limited and relatively mild, it is unlikely major investments will be made to attempt to improve the efficacy of mumps vaccines.

Pertussis

Despite decades of vaccination with first the whole-cell pertussis vaccine and, since the 1990s, acellular pertussis vaccine, pertussis is currently the least well-controlled vaccine-preventable disease in the United States. Cyclical increases are typical for pertussis, but since the 1990s the United States has experienced a continuing rise in incidence that exceeds changes due to better laboratory diagnostics or disease reporting (Fig. 14-4). The highest rates of disease, hospitalizations, and fatalities occur among infants younger than 1 year of life.[56] Reported cases in teens and older children have been increasing since 2010.[57] It has become increasingly clear that the transition from whole-cell pertussis virus vaccine "backbone" to acellular vaccines has changed the epidemiology of pertussis.

In 2010, California reported the highest rates of pertussis in 50 years. A retrospective analysis conducted there revealed vaccine efficacy was more than 95% within 3 years of receiving the last dose of acellular pertussis but decreased substantially by 5 years since vaccination.[35,58] This explained the predominance of 7- to 10-year olds in the 2010 resurgence. By 2012, high rates of disease occurred in Washington State and several other areas,[57] with surprising increases also noted among 11- and 13-year olds. Questions have been raised about whether there is differential performance of Tdap booster vaccinations among teenagers who had received acellular vaccines as young children compared with the earlier experience of teenagers who received Tdap after earlier exposure to whole-cell vaccines. Although some have speculated that bacterial strain changes noted recently might account for disease resurgence,[59] the dominant view is that acellular vaccines provide good short-term protection but provide immunity that wanes more rapidly than initially expected. Program priorities in this context are to target reduction of deaths, which mainly affect infants in the first few months of life. Hence, recent recommendations for women to be vaccinated during every pregnancy are a priority for disease control.[60]

Acute Respiratory Tract Infection

Infections involving the respiratory tract represent one of the most dynamic areas for emerging and reemerging diseases, producing dramatic examples such as the first recognized outbreaks of legionellosis in the 1970s and hantavirus pulmonary syndrome in the 1990s. Examples in the 21st century include newly recognized pathogens such as human metapneumovirus (first identified in 2001),[61] the coronavirus associated with SARS (identified in 2003),[15] human bocavirus (identified in 2005),[62] pandemic influenza A (H1N1) (identified in 2009),[16] and a Middle Eastern novel coronavirus associated with severe respiratory illness identified in 2012.[17] Other newly recognized respiratory viruses include two additional coronaviruses (NL63 and HKU1), novel human polyomaviruses KI and WU, rhinovirus groups C and D, and parechoviruses, although in some instances the role of these agents as pathogens is still being clarified.[63] More virulent strains of known respiratory pathogens have also emerged. Examples of this phenomenon include human disease associated with avian influenza viruses (especially highly pathogenic avian influenza A [H5N1] and avian influenza H7N9[18,64]), severe disease due to adenovirus type 14,[65] and extensively drug-resistant tuberculosis.[66]

Acute respiratory tract infection constitutes a broad category of diseases that include infections of both the upper and lower respiratory tracts, such as acute pharyngitis, epiglottitis, bronchitis, pneumonia, and influenza. Although upper respiratory tract infections are capable of causing severe illness, virtually all (98%) respiratory disease–related deaths are a consequence of infection of the lower respiratory tract, especially pneumonia. Acute respiratory infections remain the leading cause of mortality from infectious diseases in the United States and around the world. The World Health Organization (WHO) estimates that 4.2 million deaths resulted from lower respiratory tract infections in 2004, accounting for 7.1% of all deaths that year.[67] Among persons who died of lower respiratory tract infections, 70% (2.9 million) were residents of low-income countries. Lower respiratory tract infections are the number one cause of death in the developing world. Even in high income countries, lower respiratory tract infections are the fourth leading cause of death, responsible for 4% of all-cause mortality. Mortality from lower respiratory tract infections has the greatest impact on young children. On a global basis, 42% of all deaths from lower respiratory tract infections (mostly due to pneumonia) occur in children younger than 5 years of age.[67] Significant influenza- and pneumonia-associated mortality also occurs in persons older than 65 years of age and in individuals with chronic underlying pulmonary disease. In the United States, influenza and pneumonia are the leading cause of infectious disease–related mortality and the eighth most frequent cause of death.[68]

Human Metapneumovirus

In 2001, human metapneumovirus (hMPV) was first reported as a cause of acute respiratory tract infections when the virus was isolated

from specimens collected over a 20-year period from hospitalized children in the Netherlands with undiagnosed upper and lower respiratory tract illnesses.[61] Subsequent serologic and virologic analyses of banked specimens have demonstrated evidence of hMPV infection as far back as the 1950s, and genetic studies suggest the virus is considerably older.[61,69]

A paramyxovirus, hMPV is closely related to respiratory syncytial virus (RSV), another member of the Paramyxoviridae subfamily of Paramyxoviridae.[69,70] These related viruses have many clinical and epidemiologic features in common, and coinfections with these two pathogens have even been described.[71] Studies examining whether hMPV and RSV coinfections produce more severe illness have shown conflicting results.[71]

Since hMPV was first identified, major strides have been made in our understanding of the impact of this agent, which appears similar to other major viral respiratory pathogens. It is known to occur globally in both high- and low-income countries, and by 5 years of age virtually all children demonstrate evidence of prior hMPV infection.[72] Clinically significant illness and severe disease most commonly occur in children younger than 2 years of age, but hMPV-related illness can occur throughout childhood.[73,74] In most studies, this virus (either alone or with copathogens) has been identified in 2% to 20% of children with acute respiratory tract infections, and in 3% to 7% of children hospitalized with acute respiratory tract infections or fever.[69,73] Variation in rates of hMPV detection is likely due to patient selection criteria, sample collection, and diagnostic test methods. In contrast, hMPV is rarely (<1%) identified in children or adults who are not ill and when found is usually present in much lower titers than when detected during illness.[69,73,75] A recent multiyear, multicenter prospective study suggests that hMPV produces 20,000 hospitalizations, 263,000 emergency department visits, and 1 million outpatient visits annually among children younger than 5 years of age in the United States.[75] Because disease is also found in older children and in adults, these numbers represent an unknown proportion of the overall burden of illness due to hMPV. Multiyear studies of hMPV infection show that incidence varies from year to year and by season, with most infections in temperate locations occurring in winter and early spring.[70]

In children, most severe hMPV disease manifests as pneumonia or bronchiolitis and a substantial proportion of hospitalized children have underlying medical conditions, particularly asthma.[73-76] Intensive care can be necessary and fatal illnesses have occurred in children with hMPV infections.[77] Human metapneumovirus has also been associated with childhood upper respiratory tract infections (up to 10% in some series) as well as acute otitis media.[70]

Most infections with hMPV in adults are mild, but severe disease can occur, especially in the elderly and in persons with chronic pulmonary disease or congestive heart failure.[78,79] This virus has been estimated to involve 3% to 7% of acute respiratory tract infections and 4.5% of acute respiratory tract infection hospitalizations in adults.[79] Outbreaks associated with hMPV have been reported in both children and adults, especially among long-term institutionalized elderly, with case-fatality rates as high as 33%.[79,80] As with RSV, hMPV can produce severe and recurrent disease in immunocompromised hosts, including transplant recipients, those with hematologic malignancies, and HIV infection.[70,81] Ribavirin and immune globulin have been used to treat severe disease but have not been systematically assessed, and efforts are underway to develop candidate vaccines against hMPV.[69,82]

Genetic analyses have demonstrated two major hMPV types, designated groups A and B, with two subtypes (1 and 2) within each group; subtype variants have also been reported.[69] The geographic distribution of groups and subtypes changes over time, and multiple variants can cocirculate. Periodic shifts in predominant circulating strains are thought to coincide with upsurges in disease incidence and severity. In some studies, group A viruses have been associated with more severe disease compared with group B viruses, although other series have found the opposite result or have not suggested a difference in disease severity between the two groups.

Human Coronaviruses

Although coronaviruses were once considered to be pathogens most typically associated with the common cold, their public health significance has changed considerably in recent years.[83] The 2003 outbreak of SARS is widely considered to be the most consequential emerging infectious disease event of the early 21st century, with profound public health, economic, sociologic, and political ramifications.[84] The expanded research and monitoring of coronaviruses that resulted from the SARS episode led to the recognition of two additional human coronaviruses (NL63 and HKU1) associated with upper respiratory tract infections.[83-86] Most recently, a novel coronavirus was identified in 2012 among patients in the Middle East or patients linked to the Middle East.[17] This new virus, which is distinct from the SARS coronavirus, is also associated with severe and fatal pulmonary disease. A number of studies suggest that the human coronaviruses appear to be zoonotic in origin, with bats being especially important reservoirs.[87] Because bats harbor many coronaviruses, there is the potential for future pathogenic coronaviruses to emerge from this reservoir.

SARS was recognized in February 2003 when an explosive outbreak of adult respiratory distress syndrome was carried globally by more than a dozen individuals who were all guests at a Hong Kong hotel over a single weekend while a physician from adjacent Guangdong Province with fatal respiratory illness was also present.[88-90] Before traveling to Hong Kong, the source physician had been caring for patients with a similar illness, with 305 cases of undiagnosed respiratory diseases occurring in Guangdong Province since the previous November. A global consortium of laboratories rapidly identified the causative agent as a previously unrecognized betacoronavirus (SARS coronavirus [SARS-CoV]).[15] The outbreak was contained within 4 months of recognition, primarily through the employment of public health measures such as community isolation and quarantine.[88-90] In the interim, a total of 8,096 cases of SARS were recorded in 29 countries on five continents, with 774 (9.6%) fatalities.[91] However, 98% of the cases occurred in just five locations (Table 14-6); only 8 cases were confirmed in the United States. The following winter, four symptomatic and one asymptomatic community-acquired SARS cases occurred in Guangzhou. There was also a series of laboratory acquired infections in Taiwan, Singapore, and mainland China over the same time period.[88] No cases of SARS have been recognized anywhere in the world since 2004.

TABLE 14-6 Cumulative Number of Confirmed and Probable Severe Acute Respiratory Syndrome (SARS) Cases by Location, November 2002 to July 2003

LOCATION	NO. OF CASES	NO. OF FATALITIES	CASE-FATALITY RATIO (%)	NO. OF CASES IN HEALTH CARE WORKERS	PERCENT OF CASES IN HEALTH CARE WORKERS
China	5327	349	7%	1002	19%
Hong Kong	1755	299	17%	386	22%
Taiwan	346	37	11%	68	20%
Canada	251	43	17%	109	43%
Singapore	238	33	14%	97	41%
All others	179	13	7%	44	25%
TOTAL	8096	774	10%	1706	21%

Data from World Health Organization. Summary of Probable SARS Cases with Onset of Illness from 1 November 2002 to 31 July 2003. Available at http://www.who.int/csr/sars/country/table2004_04_21/en/index.html.

Several features of SARS are especially noteworthy. These include (1) a relatively long incubation period (mean 4.6 days, range 2 to 14 days); (2) minimal transmissibility early in the course of illness (viral shedding in respiratory secretions followed a crescendo-decrescendo pattern with peak titers on day 10 of illness); (3) a high proportion of illnesses (21%) in health care workers; (4) a low-to-moderate basic reproductive number (R0), estimated at 2 to 4 secondary cases per average infectious case[92]; (5) the occurrence of "super-spreader" events facilitated by inpatient therapeutic procedures that promoted aerosolization of the virus and accounted for much of the observed person-to-person transmission (the majority of cases resulted in no secondary transmission); (6) a rarity of asymptomatic infections; and (7) a striking age-dependent case-fatality ratio (<1% in persons <24 years of age vs. >50% in those >65 years).[88-90]

Epidemiologic investigations found that people with early SARS cases in Guangdong Province often had contact with exotic live animal markets. Several species (especially palm civet cats) in the live markets had evidence of SARS-CoV infection, leading to mass culling as a control measure.[88] The virus was not detected in these animals in the wild, and experimental infections showed the animals developed SARS-like symptoms. Both factors suggested they were not the natural host. In 2005, viruses similar to SARS-CoV (SARS-like coronaviruses [SL-CoV]) were identified in horseshoe bats in southern China and bats are now considered to represent the natural reservoir.[87,93-95] Subsequent studies have shown bats in many parts of the world harbor SL-CoVs.[87,95]

Various therapies were employed during the SARS outbreak, including ribavirin, corticosteroids, antiretroviral drugs, and immunotherapy. Some appeared beneficial, but none could be systematically evaluated.[89] SARS-CoV is known to act through a spike protein that targets angiotensin-converting enzyme 2, offering potential therapeutic options.[88,96] Vaccine development research using a variety of approaches is underway.[97]

A novel human coronavirus (initially referred to as HCoV-EMC for Erasmus Medical Center in the Netherlands and now known as Middle East respiratory syndrome coronavirus [MERS-CoV]) was first identified in July 2012 in a 60-year-old man from Saudi Arabia with fatal lower respiratory tract infection.[17] As of July 2013, a total of 81 laboratory-confirmed cases of infection with this virus have been reported internationally.[98] Cases have been reported from nine countries, all with a direct or indirect link to locations in and around the Arabian peninsula. The earliest recognized cases were retrospectively identified in 2 persons in Jordan who were part of an 11-person hospital cluster of respiratory illnesses in April 2012.[99] Of the 81 confirmed cases, the median age is 55 years (range, 2 to 94 years) and 45 (56%) have died; 64% of the cases for whom gender is known occurred in males. Illness has been characterized by severe respiratory distress and pneumonia often requiring mechanical ventilation, and some cases have been accompanied by renal insufficiency.[99] A three-person cluster in Great Britain where the index case was exposed in the Middle East and disease subsequently occurred in two close contacts in Great Britain with no history of travel, as well as an instance of nosocomial transmission in France where the index case was exposed in the Middle East, provide evidence the virus can be spread person to person.[99] In addition to the 2012 Jordanian hospital cluster, another outbreak in April 2013 involving 22 persons, including health care workers, and 9 deaths in an eastern Saudi Arabian hospital suggests nosocomial transmission.[100] Genetic analyses of this novel coronavirus show it is the first lineage C betacoronavirus infecting humans and has a close relationship to betacoronaviruses HKU4 and HKU5 found in bats, including insectivorous bat species present in the Middle East.[101-103] A virus with 100% sequence homology to the MERS-CoV isolated from the 2012 Saudi Arabian index case was found in an Egyptian tomb bat *(Taphozous perforatus)* trapped in the vicinity of that patient's home.[104] These findings suggest bats play an important role in the ecology of MERS-CoV and could be the reservoir for this new coronavirus. The virus targets a unique receptor and appears capable of infecting multiple mammalian cell lines, suggesting the potential for a zoonotic intermediary, and serologic evidence of infection with MERS-CoV has been reported in mammalian species.[105-107]

Influenza

No disease is more closely intertwined with the subject of emerging and reemerging infectious diseases than influenza.[108,109] Arguably the most dramatic example of infectious disease emergence is the 1918-1919 Spanish influenza A H1N1 pandemic. This virus swept across the globe in successive waves with profound societal disruption in the midst of World War I, leaving in its wake an estimated number of fatalities ranging as high as 50 to 100 million people.[109] In the United States alone, an estimated 675,000 deaths occurred, increasing the overall mortality rate for that period by almost 40%.[109,110] Two less consequential pandemics (caused by influenza A H2N2 in 1957 and influenza A H3N2 in 1968), but with excess mortality, also were observed in the 20th century.

Influenza has proven to be even more volatile in the 21st century. Traditional dogma regarding which influenza A hemagglutinin subtypes (H1, H2, and H3) are responsible for illness in humans has been reconsidered based on recent events. These include cases of severe human disease due to highly pathogenic avian influenza A H5N1 that have been occurring since 2003 and the increasing recognition of human disease caused by other viruses (H7, H9, H10) usually considered avian subtypes.[111-113] As the attention of the public health community was focused on the pandemic potential of these avian subtypes, in 2009 another influenza virus (a triple reassortant A H1N1) suddenly appeared in North America to produce the first pandemic of the 21st century.[114] In the aftermath of the H1N1 pandemic, a variant strain of influenza A H3N2 that produces human disease in association with swine contact, mostly at agricultural fairs, has been recognized in the United States.[115] Further complicating the picture, in early 2013 an outbreak of influenza due to avian influenza A (H7N9) virus, not known to have previously infected humans, was reported across a wide area of eastern China.[18] The novel H7N9 virus is associated with unusually high mortality in humans but is a low pathogenicity variant in poultry.[116] These examples highlight the unpredictable nature of influenza and the critical need to maintain a high state of vigilance for this disease through global surveillance in people and animals along with research to develop improved treatment, prevention, and control measures.

Avian Influenza

Human disease due to highly pathogenic avian influenza (HPAI) H5N1 was first recognized when a fatal illness occurred in a 3-year old child in Hong Kong in the spring of 1997.[117] "Highly pathogenic" is the designation used to describe avian influenza viruses with certain genetic traits that produce lethal disease outbreaks in poultry. This case was followed later in the year by a series of 18 human illnesses (6 fatal) in children and young adults that led to the mass culling of poultry in Hong Kong as a measure to control bird-to-human transmission.[118] The virus responsible for this outbreak is referred to as A/Goose/Guangdong/1/96 H5N1 because it was first identified in a goose in southern China the previous year. All subsequent human H5N1 illnesses, as well as the animal outbreaks that have led to the natural death and culling of more than 250 million poultry and wild birds, have been caused by descendants of the 1996 goose Guangdong lineage.[119,120] This virus has evolved into two major clades (1 and 2) and numerous additional clades and subtypes that have spread over three continents during sequential waves believed to originate in southern China.[119,121]

After the initial 1997 Hong Kong outbreak, episodes of human illness due to avian influenza subtypes (especially H7 and H9) were identified in Europe, Asia, and North America, producing both respiratory disease and conjunctivitis.[122-124] In early 2003, a father and son from Hong Kong who had traveled to southern China were diagnosed with H5N1 influenza at the time that the outbreak that became SARS was recognized, briefly raising concern this may have been the etiology of the outbreak.[125] However, it was not until late 2003, when SARS had subsided, that the current outbreak of H5N1 human illnesses began when cases were recognized in Vietnam and Thailand.[126,127] In contrast to previous episodes, these cases were more widely dispersed and there was evidence of widespread circulation of HPAI H5N1 in poultry, waterfowl, and wild birds in the affected areas.

Since late 2003, the virus has spread widely and has been found in 63 countries in Africa, Asia, and Europe, with more than 7000 avian outbreaks reported to the World Organisation for Animal Health.[128] HPAI H5N1 is believed to have spread through multiple modes, including bird migration, international trade in poultry and poultry products, and illegal bird transport, although the relative contribution of these modes is unclear.[111,129,130] A variety of strategies, including depopulation, enhanced biosecurity and sanitary measures, and poultry vaccination, have been employed in veterinary settings to control and prevent HPAI H5N1.[120,131,132] However, owing to the widespread distribution of this virus, its continuous evolution into multiple lineages, poultry husbandry practices in many parts of Asia, its presence in wild birds and waterfowl, and the human and financial resources needed to implement control measures, the success of these strategies has been variable.[133] Because studies in several countries have demonstrated a strong correlation between the detection of H5N1 outbreaks in poultry and the location and timing of human disease, veterinary public health measures to control the virus must remain an integral part of efforts to reduce the risk to humans from H5N1 and other avian influenza viruses.[134,135]

From 2003 through the end of 2012, the WHO has recorded 610 human cases of H5N1 in 15 countries, with 360 (59%) of these cases being fatal—an unprecedented case-fatality rate for influenza.[136] It has been argued that the observed case-fatality rate may appear artificially high owing to restrictive case definitions and surveillance methods that miss milder and asymptomatic infections.[137] However, H5N1 serosurveys, even in high-risk poultry workers, tend to yield low seroprevalence, and this argument has been challenged.[137-140] Furthermore, the case-fatality rate has not changed appreciably over time (Fig. 14-5) even as influenza surveillance, including surveillance during and after the H1N1 pandemic, has improved in affected areas. Better surveillance would likely detect less severely ill individuals.

Although human illness has been identified in 15 countries, 79% of all H5N1 cases have been reported from just three locations (Indonesia, Egypt, and Vietnam) (Fig. 14-6). This may reflect distribution of the virus in poultry reservoirs, local agricultural practices, intensity of surveillance, and other unknown factors. Between 2009 and 2012, human disease has only been found in six countries (Indonesia, Egypt, Vietnam, China, Cambodia, and Bangladesh).[136] Among countries with at least 20 reported cases, mortality has been highest in Cambodia (90%) and Indonesia (83%) and lowest in Egypt (36%). Reasons for variations in mortality are unclear, but data indicate that persons with H5N1 infections in Egypt are younger than those in other locations and overall mortality appears to be age dependent. In an analysis of a large dataset of H5N1 cases, mortality was reported to be six times higher in 10- to 29-year-olds than in children younger than 10 years old and almost five times higher in adults 30 years of age and older than in children younger than 10 years old.[141,142] Early hospitalization has also been reported to reduce mortality,[141] and observational studies have suggested that early administration of oseltamivir also reduces mortality.[64,143,144] Differences in a variety of laboratory and clinical parameters have also been described between fatal and nonfatal cases.[64,144,145] It is unclear if variation in mortality rates can be attributed to specific clades or subtypes of H5N1.

Human disease from H5N1 mainly affects children and young adults, making the high mortality especially remarkable. Among reported cases, the median age has been 18 years with a range of 3 months to 81 years.[64,141] Less than 10% of reported cases have occurred

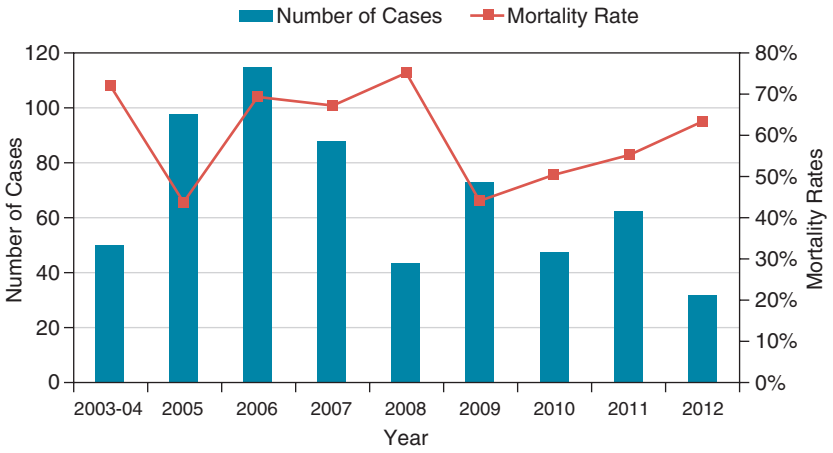

FIGURE 14-5 **Annual number of cases of human influenza A (H5N1) and associated mortality rates, 2003-2012.** *(Courtesy World Health Organization.)*

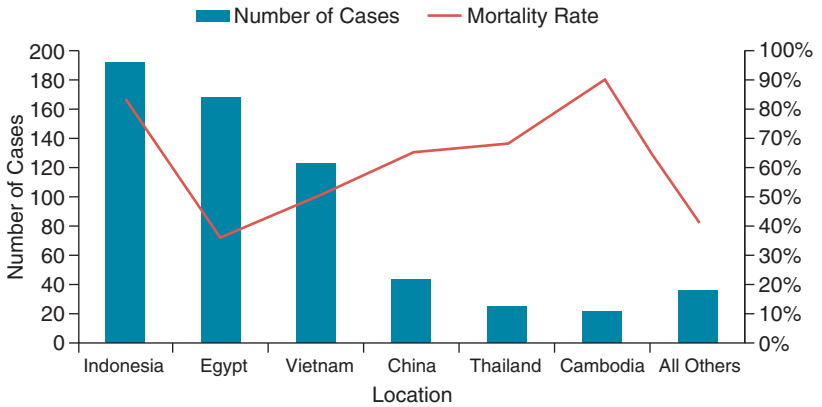

FIGURE 14-6 **Cumulative number of cases of human influenza A (H5N1) and mortality rates by country, 2003-2012.** *(World Health Organization.)*

in persons older than 40 years of age. There has been a slight female preponderance among reported cases, and cases have most commonly been seen in the winter and early spring (mirroring patterns of poultry outbreaks).[141] The incubation period has been estimated to be up to 7 days and is most typically 2 to 5 days.[64] Virtually all human cases are sporadic, with exposure to sick and dying poultry or to poultry products being the most commonly reported risk factor (96% of cases in one series).[111,141] In China, urban cases have been linked to exposure to poultry in live bird markets.[146,147] A number of small clusters indicating limited person-to-person transmission have been reported.[148] In a report summarizing the experience in Indonesia, 26 case clusters were identified with an average size of 2.5 persons; the largest involved eight members of a family with three cycles of transmission.[149]

The severity of illness, high mortality, and limited person-to-person transmissibility may be explained by the higher tropism of currently circulating H5N1 viruses to receptors in the lower but not upper respiratory tract. Most human illness has exhibited clinical and radiographic evidence of pneumonia, which is associated with substantial morbidity and mortality in influenza.[64,111] Human-to-human transmissibility is a key requirement for pandemic influenza viruses, and the ability of circulating H5N1 viruses to acquire this attribute has been of keen interest to the public health community. Two recent experiments, one through in vitro genetic reassortment and the other through site-directed mutagenesis and serial passage in ferrets, provided evidence that H5N1 can mutate in ways that facilitate transmission between ferrets, the usual surrogate for human influenza.[150,151] These "gain-of-function" experiments produced considerable debate and international alarm, resulting in delayed publication of the studies and prompting a temporary moratorium on such research until additional safeguards were in place to minimize the potential for inadvertent laboratory release or intentional misuse.[152,153] They also highlighted the need to continue preparedness efforts to develop countermeasures against H5N1 and other pandemic threats in case such mutations occur in nature. Neuraminidase inhibitors could be used prophylactically and therapeutically in the event of widespread H5N1 disease. In addition, a number of licensed pre-pandemic H5N1 vaccines have been produced by different approaches; in the United States, H5N1 vaccine is being stockpiled by the federal government as a contingency measure.[154,155]

In March 2013, an outbreak of influenza due to a previously unrecognized influenza A (H7N9) virus was detected in eastern China.[18] The earliest known illness associated with this outbreak occurred in Shanghai in February 2013 in an 87-year-old man.[18] This outbreak is notable for several unusual features. Analysis of the virus finds it to be a quadruple reassortant with all genetic segments originating in Eurasian lineage avian viruses (H7N3, H9N2, H9N7) with acquired mutations that enhance adaptation to humans.[18,116,156] The virus is of low pathogenicity to poultry and other bird species, meaning it produces minimal overt illness in bird hosts.[18] This makes it difficult to track and complicates application of control measures such as culling. Testing of avian species and environmental samples in affected areas of China found H7N9 viruses similar to those causing human illness in chickens, ducks, and pigeons, although at a very low prevalence (0.07% of 68,060 samples) given the rapid increase in recognized human cases.[157] By the summer of 2013, a total of 135 confirmed human illnesses had been detected with a 33% case-fatality rate. The number of H7N9 cases recognized after only 5 months of monitoring is higher than the greatest number of H5N1 cases seen in any year since it emerged in 1997. These H7N9 cases were found in nine contiguous eastern China provinces in addition to Beijing and Shanghai, although 79% of cases were in Shanghai and adjacent Jiangsu and Zhejiang provinces.[157] This demonstrates a wide zone of circulation in urban and rural locations either through natural spread or commercial transport and movement of poultry and other birds. An additional case was identified in Taiwan in an individual who had returned from an affected area of mainland China 3 days before illness onset.[158] As of the summer of 2013, all identified cases appeared to be sporadic except for three family clusters that could represent possible limited person-to-person spread.[159] However, monitoring of almost 1700 health care workers, family members, and close social contacts of ill individuals did not find any culture-confirmed illness to suggest that person-to-person transmission of the virus had occurred.[159]

Another unusual feature of the H7N9 outbreak is the age and gender distribution of recognized cases. The median age is 61 years (range, 2 to 91 years) with 21% of cases in persons 75 years of age or older.[158,159] In addition, males comprise 71% of recognized cases. It is unclear if these epidemiologic features result from differential exposure to the virus source or differences in population immunity, clinical presentation, or illness severity or represent surveillance artifact. However, these features stand in stark contrast to the experience with H5N1 and the 2009 pandemic, both of which predominantly impacted younger age groups.

Among H7N9 patients with available information, epidemiologic investigations suggest that most (77%), but not all, had exposure to animals (predominantly chickens and ducks) on farms or in urban wet markets.[159] Interventions that included closure and depopulation of wet markets in Shanghai coincided with a decline in newly recognized cases in that location. Clinical information on early cases indicates that virtually all (99%) required hospitalization and that most (97%) had evidence of pneumonia followed by acute respiratory distress syndrome and a majority (61%) had underlying health conditions placing them at increased risk for complications and fatal outcomes.[159,160]

Pandemic Influenza H1N1

In April 2009, two epidemiologically unlinked children living near the Mexican border in California were determined to have respiratory illness caused by a novel form of influenza A (H1N1).[161] The novel virus (referred to as pandemic H1N1 [pH1N1]) had not been previously recognized and contained six segments from influenza viruses known to be circulating in North American swine since 1998 and two segments of a Eurasian avian-like swine virus.[162] Viruses in the North American lineage that donated the segments found in pH1N1 were themselves triple reassortants, containing genetic material derived from avian, human, and classic swine viruses, and had occasionally produced human disease.[162] However, among the small number of humans identified with triple-reassortant North American swine H1 influenza, a history of close contact with pigs could usually be elicited.[163] In contrast, neither of the California children was found to have such an exposure. Both the novelty of the virus and the lack of swine contact in these children raised immediate concern that the virus was transmitted from person to person and therefore posed a pandemic threat.[16] Furthermore, only weeks earlier, Mexican health authorities had reported to the Pan American Health Organization an outbreak of severe respiratory illness associated with more than 800 hospitalizations and 100 deaths, mostly in children and young adults.[164] The same pH1N1 virus was subsequently identified in more than 40% of samples tested from Mexican patients that were part of this outbreak.[164] Epidemiologic investigations in Mexico suggested that illnesses with this virus occurred as early as February 2009 in an area of Veracruz State with nearby swine farms.[165] Within 3 weeks of its detection in the United States, more than 600 additional illnesses with pH1N1, including clusters, had been recognized in 41 states.[16] The virus was also quickly detected on other continents,[166] and by June 11, 2009, the WHO declared that an influenza pandemic due to pH1N1 was underway.[167]

Subsequent modeling studies suggest that the Mexican outbreak was much larger in scale (>30,000 cases) than initially recognized and was not nearly as severe as first reported, with an estimated case-fatality rate of only 0.4%.[165] There is also evidence that pH1N1 spread quickly from its initial focus in Mexico to other locations. Among early cases in the United States, 18% had a history of recent travel to Mexico, and early cases in Europe and elsewhere had a similar travel history.[16,166] A modeling analysis also suggested a strong relationship between air passenger traffic to and from Mexico and locations that had early importations of pH1N1.[168] By late May 2009, pH1N1 was already reported from 48 countries and the total number of identified cases was escalating quickly. Once the pandemic was declared over, a total of 214 countries, overseas territories, or communities worldwide had reported cases of pH1N1.[169]

In the United States, the pandemic occurred in two waves: a spring wave was followed by a much larger autumn wave, which peaked in late October.[170] During the pandemic period, more than 99% of all subtyped influenza viruses in the United States were pH1N1.[170] The fall

wave did not begin simultaneously throughout the country, and analyses suggest that its timing in a location correlated with the beginning of the school year.[171] Schools appeared to play an important role in community spread of the virus.[172] A number of countries, including the United States, promulgated school closure policies, and observational studies suggest these policies led to reductions in transmission and in the occurrence of respiratory illness.[173-175]

Using a variety of data sources, the Centers for Disease Control and Prevention (CDC) estimates that between 43 million and 89 million (mid-range 61 million) illnesses due to pH1N1 occurred over the course of the pandemic (April 2009 to April 2010) in the United States, representing between 14% and 29% of the population based on 2010 U.S. census data.[176] These proportions are not substantially different from those reported in other parts of the world.[177] In the United States, these illnesses led to an estimated 274,000 hospitalizations (range, 195,000 to 403,000) and 12,470 deaths (range, 8,870 to 18,300), with a resulting hospitalization rate of 0.45% and case-fatality rate of 0.02.[176] However, these illnesses were not equally distributed by age. Children and young adults were disproportionately impacted by the pH1N1 pandemic, with 33% of all cases occurring in those younger than 18 years of age. In contrast, only 10% of all cases occurred in persons in the 65 and older age group. The estimated overall attack rate in children was 26%, and in persons older than 18 years it was 18.5%.[178] In contrast to mortality patterns with seasonal influenza, where 90% of all deaths occur in persons older than age 65 years, 87% of all influenza-related deaths in the United States during the pandemic were in persons younger than age 65 years and the median age of death was 37 years.[178,179] However, the case-fatality rate was estimated to be more than four times higher in persons older than 65 years of age than in children younger than 18 years of age.[178] Globally, the estimated number of respiratory and cardiovascular deaths associated with pH1N1 was 284,500 (range, 151,700 to 575,500), with 80% of these deaths in persons younger than 65 years of age.[180]

Serologic surveys performed in multiple locations support the findings of a higher incidence of infection in children and teenagers (20% to 60%) than in older age groups.[181] These surveys also found that the presence of cross-protective immunity in pre- or early-pandemic specimens was age dependent, being very low in children and peaking in persons older than 60 years, and suggest that older individuals were protected during the pandemic by residual immunity from exposure to pre-1950s cross-reactive H1N1 viruses.[181] Another study that examined laboratory-confirmed pH1N1 infections and hospitalizations found a marked decline in risk for persons born in the 1950s and attributed this reduction to exposure to H1N1 viruses circulating before the 1957 Asian H2N2 pandemic.[182]

The clinical features of illness from pH1N1 were typical of those seen with seasonal influenza, with fever and cough most common (Fig. 14-7) and an incubation period estimated to be 1.5 to 3 days (upper range, 7 days).[177,183] The incubation period was similar to estimated serial intervals (mean, 2.6 to 3.9 days) for spread of illness in households, where the estimated secondary infection rate reported in studies varied from 3% to 38%; higher secondary infection rates were seen in children than in adults.[184] The basic reproductive number (R_0, the number of additional cases generated by each infection) was estimated at 1.3 to 1.7 (which is slightly higher than seasonal disease), although reproductive numbers as high as 3.3 were found in some school settings.[183]

The most common severe complication during the pandemic was viral pneumonitis or secondary bacterial pneumonia.[183] Several groups were notably at higher risk for developing severe and fatal illness. These include pregnant women, especially in the third trimester of pregnancy, which accounted for half of the hospitalizations of pregnant women.[185] Whereas approximately 1% of the population is pregnant at any time, pregnant women accounted for 6.3% of hospitalizations, 5.9% of intensive care unit admissions, and 5.7% of deaths during the pandemic and had a relative risk for hospitalization of 6.8 compared with all women of childbearing age.[185,186] Obesity, particularly morbid obesity (body mass index >40), was also found to be a risk factor for severe disease. In the United States, morbidly obese persons with no other chronic medical conditions had a statistically significant odds of hospitalization of 4.9 and an odds of death if hospitalized of 7.6 compared with nonobese persons.[187] In a global pooled data analysis, the relative risk of death among the morbidly obese was 36.3.[186] The increased risk for severe outcomes in both pregnant women and obese persons is likely multifactorial but could include relative immune suppression or impaired pulmonary function. Another high-risk group for severe illness was children with neurologic disease. In the United States, 43% of fatalities in those younger than 18 years of age had neurologic disease; 94% of these children had neurodevelopmental disorders such as cerebral palsy and intellectual impairment.[188]

A variety of nonpharmaceutical interventions, including school closure, were implemented to mitigate the impact of the 2009 influenza pandemic. Once pH1N1 was recognized to pose a pandemic threat, efforts were immediately initiated to develop monovalent vaccines. Trials in the United States showed that candidate vaccines produced using standard methods were immunogenic and safe, and large-scale production was initiated under government purchase and distribution.[189] Priority groups for vaccination representing 159 million persons were identified by the Advisory Committee for Immunization Practices and the CDC, and a more limited priority group of 62 million persons was identified for the anticipated initial limited vaccine supply (Table 14-7). Ultimately, the first vaccine supplies did not become available until the beginning of October 2009, only weeks before the second wave of illness peaked. This was too late to have a substantial short-term impact, and allocation and distribution of limited supplies were challenging.[189,190] Pandemic vaccine was shown to have a safety profile

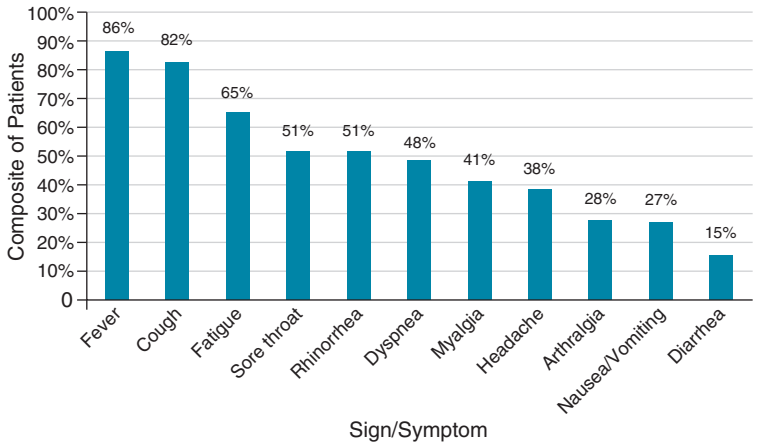

FIGURE 14-7 Composite of signs and symptoms reported by 11,334 patients with laboratory-confirmed pandemic influenza A (H1N1). Data are from multiple locations and surveys and involve outpatients, hospitalized patients, and specific settings, exclusively or in combination. The number of patients in each category reporting presence or absence of symptoms varies. *(From Cheng VC, To KK, Tse H, et al. Two years after pandemic influenza A/2009/H1N1: what have we learned?* Clin Microbiol Rev. *2012;25:223-263.)*

similar to seasonal trivalent influenza vaccine, and studies generally showed 70% to 90% effectiveness against laboratory-confirmed disease.[189,191] Through the end of 2009, approximately 81 million doses of vaccine were shipped and 61 million doses were administered, with 74% given to priority targeted groups.[192] Neuraminidase inhibitors were widely employed for treatment, with an estimated 8.2 million prescriptions filled during the pandemic.[193] Investigational intravenous peramivir and zanamivir were also successfully used in almost 1500 persons in the United States.[194,195] A number of observational studies demonstrated that antiviral drugs administered early in the course of illness reduced adverse outcomes.[196]

The pandemic influenza A (H1N1) virus has continued to circulate since the pandemic was declared over by the WHO in August 2010.

TABLE 14-7 Priority Groups Recommended for Vaccination during the 2009 Influenza A (H1N1) Pandemic by the Advisory Committee for Immunization Practices and the Centers for Disease Control and Prevention

RISK GROUP	LIMITED SUPPLY RISK GROUP	RATIONALE FOR PRIORITIZATION
Pregnant women	Pregnant women	Higher risk for complications; protection of infants
Household contacts and caregivers of infants aged <6 mo	Household contact and caregivers of infants aged <6 mo	Infants at higher risk for complications and cannot receive vaccine
Health care and emergency service personnel	Health care and emergency service personnel with direct contact with patients or infectious material	Higher risk for exposure; potential exposure of higher-risk patients; reduced absenteeism
Persons aged 6 mo-24 yr	Children aged 6 mo-4 yr	Higher disease burden and transmission
Persons aged 25-64 yr with medical conditions placing them at higher risk for influenza complications	Children 5-18 yr with medical conditions placing them at higher risk for influenza complications	Higher risk for complications

The first column includes priority groups for vaccination representing 159 million persons; the second column includes a limited subset of priority groups for vaccination during periods when vaccine supply is limited representing 62 million persons.

Data from Centers for Disease Control and Prevention. Use of influenza A (H1N1) 2009 monovalent vaccine, recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep. *2009;58(RR-10):1-8.*

Variant Influenza A (H3N2)

In 2012, a multistate outbreak of influenza caused by a swine-origin (variant) influenza A (H3N2) virus occurred in the United States, with 307 recorded cases in 11 Midwestern and Middle Atlantic states.[197] Additional single cases were identified in Utah and Hawaii. The resulting illness had typical clinical features of influenza; 16 cases (5%) required hospitalization and one fatality occurred in an adult.[197] However, most cases (93%) were recognized in persons younger than 18 years, and the median age was 6 years. The outbreak occurred between July and September during the major period when agricultural and state fairs that exhibit swine occur.[198] Most ill persons (>90%) had a history of participation in or attendance at these events, with a history of direct or indirect contact (often sustained) with swine, and there was evidence of only limited person-to-person transmission.[198] Similar H3N2v viruses were identified in exhibited swine in some locations.[198] In response, the CDC recommended that persons at high risk for complications of influenza, including individuals younger than 5 and those 65 years of age and older, avoid contact with swine or swine barns at agricultural fairs during 2012.

The variant H3N2 virus is a descendent of a lineage of a triple-reassortant H3N2 virus with human, avian, and swine segments that began widely circulating in North American pigs in 1997-1998.[199] The first human infection caused by this variant was not recognized until 2005 in Kansas, and only sporadic human cases were recognized before 2011.[200] In 2010, the virus was observed to have acquired the M (matrix) segment from the pandemic H1N1 virus (Fig. 14-8) and to have become more frequent in swine, raising concerns about enhanced transmissibility and an increased burden of disease in humans.[201] After that reassortment event was recognized in swine, 12 human cases were recognized in 2011 in five states.[202] Similar to the larger 2012 outbreak, disease occurred mostly in children and agricultural event exposure was prominent with limited person-to-person transmission.[203] Serologic studies demonstrated little cross-protective immunity in young children.[204] In contrast, a significant proportion of older children and adults appeared to have such immunity, likely owing to similarities with H3N2 viruses that circulated in the 1990s and earlier.[204] Studies show that current trivalent influenza vaccines offer little protection against the variant H3N2 virus.[204] The emergence of this virus provides a further demonstration of the critical role swine play in influenza

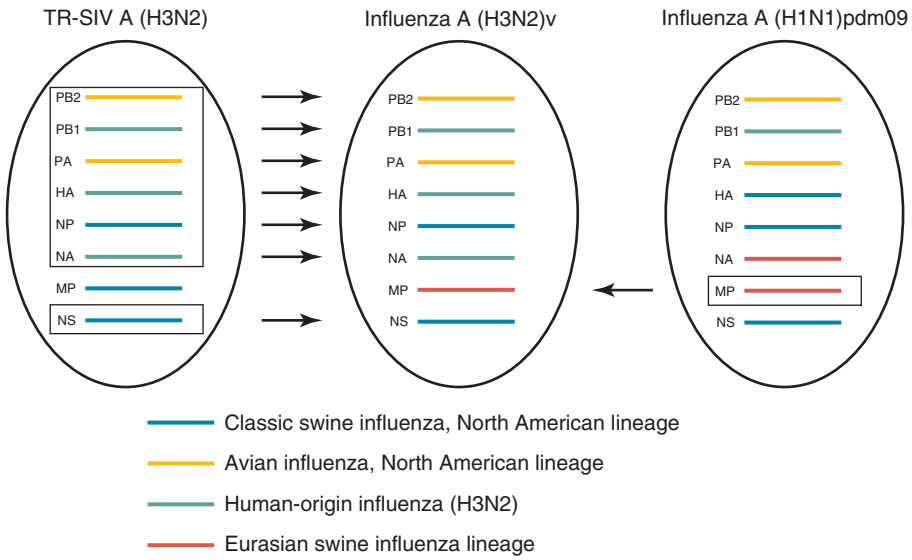

FIGURE 14-8 Origins of gene segments of novel influenza A (H3N2) viruses isolated from humans, United States, in 2011-2012. *(From Lindstrom S, Garten R, Balish A, et al. Human infections with novel reassortant influenza A (H3N2)v viruses, United States, 2011.* Emerg Infect Dis. *2012;18:834-837.)*

virus evolution and the need for a "One Health" approach to influenza prevention and control (see "Vector-borne and Zoonotic Diseases").

Human Bocaviruses

Human bocaviruses were first detected in 2005 in Sweden when investigators used molecular virus screening methods by taking cell-free, filtered supernatants of stored respiratory specimens looking for virus-sized particles and then performing random polymerase chain reaction (PCR) amplification of the genetic material.[62] Among the sequences identified was a previously unrecognized parvovirus most closely related to animal viruses of the genus *Bocavirus*. Since the original identification of bocavirus DNA in respiratory specimens, three additional bocaviruses have been found in stool specimens; these agents are now referred to as HBoV1 to HBoV4. HBoV2 to HBoV4 are believed to be associated with gastrointestinal illness, whereas HBoV1 causes predominantly respiratory disease.[205]

Human bocaviruses have been challenging to study because of the lack of in vitro or animal models. However, numerous studies suggest HBoV1 can be found in 2% to 19% of patients with acute respiratory tract infections, and, as often as 83% of the time, is present with other coinfecting respiratory pathogens.[205,206] This latter finding calls into question whether HBoV1 is a pathogen, especially because HBoV1 has been shown to persist in respiratory specimens for months after acute infection, meaning it can be detected in asymptomatic individuals.[205,206] However, in most studies HBoV1 has been found more commonly in children with acute respiratory disease than asymptomatic children; copy numbers of the virus are higher in monoinfections than coinfections and are usually low in asymptomatic children. Serology also suggests HBoV1 is a pathogen.[205-207] Children aged 6 to 24 months are most commonly infected; serologic studies show that almost all children have evidence of previous HBoV1 infection by 6 years of age.[205,207] Illness is most common in winter. Infection can produce either upper or lower respiratory tract infection and in children is often accompanied by wheezing; pneumonia and bronchiolitis can also be seen.[205,206,208] Of note, DNA has been detected in serum and urine of children with acute infections, suggesting systemic infections can occur.[205]

Diarrheal Disease

Diarrheal disease is the second leading cause of infectious disease morbidity and third leading cause of mortality worldwide, resulting in an estimated 90 million disability-adjusted life years and 1.4 million deaths in 2010.[5,6,209] Although diarrheal disease affects persons of all age groups and in all geographic locations, the greatest burden of severe illness and death falls on infants and young children in developing countries. In 2010, diarrhea ranked third behind malaria and lower respiratory tract infections among the leading causes of death in children younger than 1 to 4 years of age. Undernutrition is an important underlying cause of many of these deaths.[210]

Diarrheal disease also produces substantial morbidity, affecting growth and cognitive development[211,212] and resulting in illness of more than 2 weeks in duration in 10% of cases.[213] Studies among children in developing countries have found a range of 1 to 10 episodes of diarrhea per child each year, with most children experiencing 3 to 5 episodes per year.[214,215] A survey among the general U.S. population reported a rate of 1.4 episodes of diarrhea per year, translating to 200 to 375 million episodes annually.[216]

The pathogens that produce diarrhea are transmitted primarily by three main routes: foodborne, waterborne, and person to person; many enteric pathogens can be transmitted by more than one route, including simultaneously. Although systematic studies are difficult to perform, it is likely that the relative importance of these transmission patterns varies in different settings. Estimates in the United States suggest that 48 million episodes of foodborne illness occur annually, resulting in approximately 128,000 hospitalizations and approximately 3,000 fatalities[217,218] and that endemic waterborne disease results in 4.3 to 32.8 million cases of acute gastrointestinal illness annually.[219,220]

The pathogens that cause diarrheal illness differ in their primary modes of transmission. For example, nontyphoidal *Salmonella* species and *Campylobacter jejuni* are transmitted principally through food, *Shigella* species are transmitted primarily from person to person, and *Cryptosporidium parvum* is principally waterborne. Determination of the patterns of distribution of enteric pathogens in a geographic area may suggest the relative importance of different modes of transmission in that locale.

The causes of diarrheal disease do not remain static over time, even in a single location. Fluctuations may result from the introduction of an organism not previously present, the recognition of a new agent, changing levels of sanitation resulting from man-made or natural disasters, climatic variations, or lifestyle changes, such as increases in recreational water exposure.[221,222] Two dramatic examples from the past 25 years involve the introduction of *Vibrio cholerae* O1 into the Western Hemisphere. Cholera had not been recognized in South America during the 20th century, but in January 1991 cases were identified in coastal areas of Peru.[223] Within weeks, thousands of cases were occurring and cholera quickly became the most commonly diagnosed cause of diarrheal illness in many parts of Peru.[224,225] During the next 3 years, the disease spread throughout mainland South and Central America, significantly altering the distribution patterns of etiologic agents of diarrheal disease. The incidence of the disease in Latin America has subsequently declined dramatically.

In October 2010, just 9 months after a severe earthquake, a cholera epidemic was identified in Haiti that spread within 2 months to the entire country and across the border to the Dominican Republic.[226,227] Molecular epidemiologic studies have indicated that the *V. cholerae* strain is very similar to South Asian strains,[228] and epidemiologic investigations revealed that initial cases occurred downstream from a camp where United Nations peacekeepers from Nepal were stationed.[229,230] The source of introduction of the epidemic strain remains a politically sensitive topic.[231] Although the case-fatality rate has been reduced, the epidemic persists.[232] Cases in Haiti and the Dominican Republic accounted for more than 60% of the global reported cases to the WHO in 2011.[233] In addition to cases in the Dominican Republic, imported cases have been identified in the United States[234] and elsewhere in the Western Hemisphere.[233]

V. cholerae O139 is an example of a recently recognized pathogen that had a major impact on the distribution of diarrheal disease–producing pathogens in Asia. This serotype was first detected in South Asia in 1992 and quickly spread to many regions of India and Bangladesh.[235,236] Studies conducted in Bangladesh suggested that shortly after its introduction *V. cholerae* O139 became the agent most commonly linked to clinical cholera in that country. Since then, its impact has fluctuated in place and time throughout South and Southeast Asia[236-238]; in 2011, only China reported cases to the WHO.[233]

One other emerging issue with *V. cholerae* merits mention. Variant El Tor strains that express the cholera toxin produced by classic strains resulting in more severe illness have been identified, initially in Bangladesh and more recently elsewhere in Asia, Africa, and Hispaniola.[233,239]

The international movement of foods can also alter the spectrum of diarrheal pathogens. In 1996, thousands of cases of cyclosporiasis due to *Cyclospora cayetanensis* occurred in the United States and Canada among persons who consumed fresh raspberries imported from Guatemala.[240] Before this episode, only small numbers of cases, primarily associated with travel to developing countries,[241] had been reported in North America. In 2008, a large nationwide foodborne outbreak caused by *Salmonella enterica* serotype Saintpaul occurred in the United States. Initial investigation suggested that contaminated tomatoes imported from Mexico were the source. However, subsequent investigation implicated jalapeño and serrano peppers from Mexico.[242]

International spread of a multidrug-resistant clone of *S. enterica* serotype Kentucky with high-level resistance to ciprofloxacin has been reported.[243] The clone appears to have originated in Egypt during the 1990s and has spread to other countries in Africa and the Middle East. Cases that are predominantly travel associated have also been identified through national surveillance systems in France, England and Wales, Denmark, and the United States.[243]

Escherichia coli O157:H7 (Shiga toxin [ST]-producing strains [STEC]) significantly affected pathogen distribution patterns in developed parts of the world after the agent was first recognized.[244] After its recognition in the United States in 1982, this foodborne agent rapidly became the most commonly identified cause of bloody diarrhea in

many locations in North America.[245] Surveys conducted in the 1990s and in 2007 found it was the fourth most commonly isolated bacterial agent of diarrheal disease in the United States.[245,246] In 2012, STEC non-O157 strains ranked fifth and STEC O157 strains ranked sixth in incidence per 100,000 population among laboratory-confirmed cases of foodborne infections in the 10 states participating in the Foodborne Diseases Active Surveillance Network (FoodNet).[247]

In early May 2011, a large outbreak of bloody diarrhea and hemolytic-uremic syndrome was recognized in northern Germany.[248,249] Investigation identified a unique single clone of *E. coli* O104:H4 as the etiologic agent.[249,250] The strain contained a prophage encoding Shiga toxin 2, genes from enteroaggregative *E. coli,* and a plasmid-encoded extended spectrum β-lactamase gene.[249,251] Epidemiologic investigation identified fenugreek sprouts as the food vehicle[252,253]; the sprouts were grown from seeds of Egyptian origin.[249] The outbreak involved more than 4000 illnesses, primarily in adults,[254] approximately 800 cases of hemolytic-uremic syndrome (HUS), and 50 deaths in Germany and 15 other countries[249] and provides yet another reminder of the global nature of today's food supply.

Outbreaks of diarrheal diseases are particularly affected by deteriorations in public health infrastructure, as dramatically illustrated by the introduction of cholera into Haiti after the 2010 earthquake. Shigellosis is known to emerge rapidly in areas with social disruption caused by war and political unrest, especially when large numbers of refugees have lacked access to water and sanitation services.[255] As a result of the Rwanda crisis in 1994, cholera outbreaks in the refugee camps in Goma, the Congo, caused at least 48,000 cases and 23,800 deaths within 1 month.[256] Similarly, a large cholera outbreak occurred in Zimbabwe in 2008-2009 during a period of political turmoil and economic collapse.[257,258] The disease spread across borders to South Africa, Botswana, and Mozambique.[258]

Viruses are an increasingly recognized cause of sporadic and outbreak-associated diarrheal diseases. Noroviruses (members of the Caliciviridae) are transmitted not only from person to person but also by food and water and by contact with contaminated environmental surfaces.[259-261] These viruses have become an important cause of diarrheal illness outbreaks among cruise ship passengers, hospitalized patients, nursing home residents, college students, restaurant patrons, and military personnel, reflecting the high infectivity and low infectious dose (<20 viral particles).[262] A systematic literature review published in 2008 indicated that severe norovirus disease occurs among persons in both developed and developing countries, annually resulting in an estimated 64,000 episodes of diarrhea requiring hospitalization and 900,000 clinic visits by children in developed countries and as many as 200,000 deaths among children younger than 5 years of age in developing countries.[263] Noroviruses are the leading cause of epidemic gastroenteritis in the United States.[264,265] After the introduction and use of rotavirus vaccines, noroviruses have also become the leading cause of medically attended acute gastroenteritis in U.S. children younger than 5 years of age; these viruses were found in 21% of children seeking medical care for acute gastroenteritis in 2009-2010.[266] New strains emerge every few years. In March 2012, a new GII.4 norovirus strain named GII.4 Sydney was identified in Australia and subsequently spread to the United States, United Kingdom, and a number of other countries.[267] GII.4 norovirus outbreaks have been associated with higher rates of hospitalization and mortality compared with outbreaks caused by other genotypes.[268]

Because the pathogens responsible for diarrheal disease vary over time, even in the same location, longitudinal studies are important for defining the etiology of diarrheal disease. Data from the Global Enteric Multicenter Study (GEMS) conducted using standardized methods[269-271] over 3 years in seven developing countries in Africa and Asia indicated that the leading pathogens in children younger than 5 years of age with moderate to severe diarrhea across all sites were rotavirus, *Cryptosporidium,* enterotoxigenic *E. coli* strains producing heat-stable enterotoxin, and *Shigella.*[272] Compared with control children, those with moderate-to-severe diarrhea had an 8.5-fold increased risk for death during follow-up.[272]

Rotavirus infections affect all age groups and have been the leading cause of severe acute diarrhea among young children worldwide.[273] Most severe illnesses and hospitalizations occur in children younger than age 2 years, who often develop dehydrating diarrhea from the infection.[274,275] As recently developed rotavirus vaccines are introduced into more countries in Africa and Asia, the impact of rotavirus infection on the total diarrheal disease burden will decrease.

Rotavirus is also an important cause of childhood diarrhea and hospitalization in developed countries.[274] In the United States in recent years, rotavirus infection has resulted in an estimated 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 physician visits and has caused an estimated 20 to 60 deaths per year.[276] After licensure of a new rotavirus vaccine and recommendations for its use in infants in early 2006, surveillance indicated that the 2007-2008 rotavirus season had a delayed onset and a reduction in disease burden.[277] A recent study during the 2009-2010 and 2010-2011 rotavirus seasons documented the effectiveness of both rotavirus vaccines in reducing the risk for emergency department visits and hospitalizations combined in children younger than 5 years of age.[278] As a result, noroviruses have now replaced rotaviruses as the leading cause of medically attended gastroenteritis in U.S. children.[266]

Systematic studies in the United States indicate that among the bacterial diarrheal pathogens, *C. jejuni* was the most commonly diagnosed agent in the early 1990s, followed by nontyphoidal *Salmonella* species, *Shigella,* and *E. coli* O157:H7.[245] More recent data from FoodNet sites for 2012 indicate that *Salmonella* serotypes are now the most common bacterial pathogen, followed by *Campylobacter* and *Shigella.*[247] In 2012, the incidence of *E. coli* serotypes other than O157:H7 exceeded that of *E. coli* O157:H7 strains. The incidence of *Campylobacter* and *Vibrio* infections was higher in 2012 compared with that in 2006 to 2008, while the incidence of infections caused by most major foodborne bacterial pathogens was unchanged.[247] Continued surveillance along with detailed information on patient exposures and strain subtypes can help assess the impact of control measures on *Campylobacter* infections, including new standards for chicken and turkey processors issued by the U.S. Department of Agriculture in 2011. In addition, despite a significant increase in *Vibrio* infections, the number of these infections continues to be low.[247,279]

Foodborne sources remain an important cause of bacterial diarrheal disease in the developed world, because all but *Shigella* species are transmitted principally through foods. Notifiable disease data demonstrate trends in the occurrence of these pathogens but severely underestimate their incidence. As an example, 45,970 cases of salmonellosis were reported in the United States in 1995 but estimates suggest that almost 2 million U.S. infections with the bacteria occur each year.[280]

The incidence and severity of *Clostridium difficile*–associated disease has recently increased dramatically in adults and children in the United States, Canada, Europe, and Australia.[281-284,285] In the United States during 2010 in Emerging Infections Program sites, 94% of *C. difficile* infections were health care associated whereas 6% occurred in patients with no recent health care setting exposure.[283] Disease due to a strain of restriction endonuclease analysis group BI, pulsed-field gel electrophoresis type NAP1, and PCR ribotype O27 (BI/NAP1/O27) is responsible for much of this increase, including many nosocomial outbreaks.[286-288] Two distinct epidemic lineages, both of which are resistant to fluoroquinolone antibiotics, have recently been identified.[284] The FQR1 lineage, first seen in 2001, is associated with North American outbreaks and sporadic infections in South Korea and Switzerland. The FQR2 lineage originated in 2003 in North America but subsequently spread more widely, causing hospital outbreaks in the United Kingdom, continental Europe, and Australia.[289] Of the HAIs, 75% of persons had onset of illness outside acute care hospitals (in the community or in nursing homes).[289,290] These strains can cause severe disease, particularly in elderly patients. Since 2005, another *C. difficile* strain (PCR ribotype O78) has emerged in the Netherlands and in the United Kingdom.[291] This strain also appears to be hypervirulent and is more likely to affect younger persons and to be associated with community-onset disease.[291] Isolates of *C. difficile* also have been obtained from retail ground meat samples,[292] prompting the need for evaluation of the potential role of foodborne transmission in community-associated cases. Recent experiences with fecal microbiota transplantation have suggested an important role for this approach in the management of patients with severe *C. difficile* infections.[293,294]

Multiple drug resistance in bacterial enteric pathogens has emerged in the United States and internationally. The problem is most severe in foodborne pathogens of animal origin (primarily in *Campylobacter* and *Salmonella* strains).[295] A multidrug-resistant strain of *S. enterica* serotype Typhimurium known as definitive type 104 (DT104) emerged in the United States and Europe in the 1990s.[296,297] Patients infected with multiply-resistant strains are more likely to be hospitalized.[298] Fluoroquinolone-resistant strains of *C. jejuni* infections have also emerged; some infections are associated with foreign travel whereas others are acquired domestically and have been associated with poultry consumption.[299] In a study of resistance in over 1100 *Shigella* isolates in FoodNet sites from 2008 to 2010, 74% were resistant to ampicillin, 36% to trimethoprim-sulfamethoxazole, 28% to tetracycline, and 0.5% to ciprofloxacin[300]; 5% of isolates were resistant to five or more antimicrobial agents.[300] Resistance was more common in persons with a history of recent foreign travel. A foodborne outbreak in Los Angeles in 2012 was caused by *Shigella sonnei* with decreased susceptibility to azithromycin, the first such outbreak identified in the United States.[301]

The global pattern of diarrheal disease is likely to continue to evolve, and efforts to develop effective vaccines against causative agents are ongoing. New formulations of rotavirus vaccine have been developed after an initial tetravalent rhesus/human reassortant rotavirus vaccine was linked to intussusception in infants and was withdrawn from the market.[302] These new rotavirus vaccines have the potential to decrease the burden of diarrheal disease among persons in the developing world, and a major effort is in progress to introduce these vaccines into all national immunization programs as recommended by the WHO.[303] In addition, food production practices are changing, with greater amounts of fresh fruits and vegetables grown in the developing world for export to developed countries. Such practices have resulted in the transfer of agents such as *C. cayetanensis, V. cholerae,* and *S. enterica* serotype Enteritidis in exported products—a situation that is likely to continue.[240,304,305] Changes in food distribution practices increase the potential for widespread, multinational disease outbreaks. The increasing numbers of immunocompromised individuals who are at risk for infections with a broader array of pathogens responsible for diarrheal illness and increasing global travel will likely influence future trends in diarrheal disease in ways that may be difficult to predict.[306,307]

Another example is the emergence of a new strain of multidrug-resistant *S. enterica* serotype Typhimurium (multilocus sequence type ST313) in sub-Saharan Africa. The strain causes invasive nontyphoidal disease, sometimes accompanied by diarrhea, primarily in patients with HIV infection, malaria, and malnutrition.[308,309] Application of whole-genome sequence-based phylogenetic methods has identified two closely related, highly clustered lineages estimated to have emerged independently approximately 52 and 35 years ago. Lineage II strains have replaced lineage I strains, perhaps because of their acquisition of chloramphenicol resistance.[309]

Climate change has been reported to affect the spread of cholera and *Vibrio parahaemolyticus* infections. In 2004, a large outbreak of *V. parahaemolyticus* infection associated with consumption of raw oysters occurred among passengers aboard a cruise ship in Prince William Sound in Alaska.[310] The oysters were harvested in the Sound during summer months when daily water temperatures exceeded 15° C. This outbreak extended by 1000 km the northernmost documented source of oysters associated with *V. parahaemolyticus* infection.

Efforts to decrease the emergence and enhance the control of diarrheal disease and associated antimicrobial resistance in the United States and internationally require strengthened disease surveillance systems to monitor disease trends and changes in food consumption patterns. Advances in molecular diagnostic techniques for rapid diagnosis and characterization of isolates[311,312] offer advantages over current techniques, but the shift to this new paradigm away from pathogen isolation will pose challenges in the near term for many current infectious disease surveillance systems that rely on characterization of bacterial isolates.[313,314] Interstate foodborne disease outbreaks will continue to pose challenges,[315-317] as will the international spread of drug-resistant enteric pathogens.[243] The role of food in the transmission of drug-resistant organisms will require continued attention.[318] The potential importance of several enteric pathogen candidates such as enterotoxigenic *Bacteroides fragilis,*[319] *V. cholerae* serogroups O75[320] and O141,[321] bocavirus species HBoV2,[322] *Klebsiella oxytoca* in patients with antibiotic-associated diarrhea[323] and hemorrhagic colitis,[324] and enterohemorrhagic *E. coli* O26:H11/H− strain recently identified in Europe[325] require further evaluation. Use of advanced molecular diagnostics and other emerging technologies may be useful in assessing the role of currently unrecognized etiologic agents and alterations in the intestinal microbiome in patients with sporadic unexplained diarrheal illness and Brainerd diarrhea.[326,327] Patients who develop traveler's diarrhea while abroad[306,307] and those who develop unexplained diarrhea in hospital settings[328] represent ideal sentinel populations for further study to identify additional etiologic agents. Certain high-risk foods such as raw milk[329] and unpasteurized cheeses[330,331] require continual attention from public health authorities. Because recent antimicrobial exposure has been identified as a risk factor for acquisition of enteric infections in animal models[332] and in humans,[333,334] continued emphasis on judicious antimicrobial use is critical. Finally, because human contact with animals and their environments remains an important mode of acquisition of important enteric pathogens, especially *Salmonella, Campylobacter,* and *Cryptosporidium,*[335-339] increased interdisciplinary collaborative efforts at the human, animal, environmental interface as promoted by the "One Health" model are a priority (see "Vector-borne and Zoonotic Diseases").

VECTOR-BORNE AND ZOONOTIC DISEASES

Most of the emerging infections recognized during the past decade have been zoonoses (see Table 14-2).[3,340] Some zoonotic microbes have "jumped" from animals to humans to become major human pathogens (e.g., the simian virus that evolved into HIV[341]), whereas others are maintained in animal reservoirs, including domesticated animals (e.g., cattle infected with Rift Valley fever virus[342]) or wildlife (e.g., bat species that carry Nipah or Hendra viruses[343] and monkeys and rodents that carry monkeypox[344]). Bats have become an increasingly important source of emerging infections and have been linked to SARS coronavirus as well as Nipah, Hendra, and Ebola and Marburg viruses. Some vector-borne diseases are also zoonotic (e.g., West Nile disease, caused by a mosquito-borne virus maintained in birds, or Lyme disease, caused by a tick-borne bacteria maintained in deer and rodents), whereas for others humans are the principal host (e.g., dengue and human species of malaria).

Emerging public health concerns related to vector-borne and zoonotic infections include the geographic spread of mosquito-borne diseases such as dengue, chikungunya, and West Nile fever, the rising incidence of tick-borne infections such as Lyme disease, and recurring outbreaks of Ebola and Marburg hemorrhagic fever in Uganda and the Democratic Republic of the Congo.[345] In addition, animal influenza strains that cause disease in humans (e.g., avian influenza A [H5N1],[346] avian influenza A [H7N9],[18,347] and influenza A [H3N2] variant virus[203,348]) remain ongoing concerns because of their potential to evolve into pandemic strains. The origin and reservoir of a recently identified coronavirus, named Middle Eastern respiratory syndrome coronavirus (MERS-CoV), although presumed to be a zoonotic infection, has not yet been identified (see "Acute Respiratory Tract Infection").

The recognition that the majority of new human pathogens emerge from animal reservoirs has led to increased medical, veterinary, and scientific support for a "One Health" approach to infectious disease control, a growing consensus about the importance of intensifying efforts to link infectious disease identification, prevention and control at the human, animal, and environmental interface.[349,350] Areas of "One Health" focus include identifying emerging drug resistance in zoonotic pathogens that infect domestic animals and humans; evaluating the efficacy of veterinary vaccines in reducing the incidence of animal pathogens that can infect humans (e.g., Rift Valley fever virus[351]); and developing new methods and strategies to prevent infections carried by ticks or mosquitoes.

Public health and animal health scientists are also exploring strategies for predicting and preventing the emergence of novel zoonotic pathogens, making use of pathogen discovery tools and mathematical modeling techniques.[352] These efforts require detailed understanding

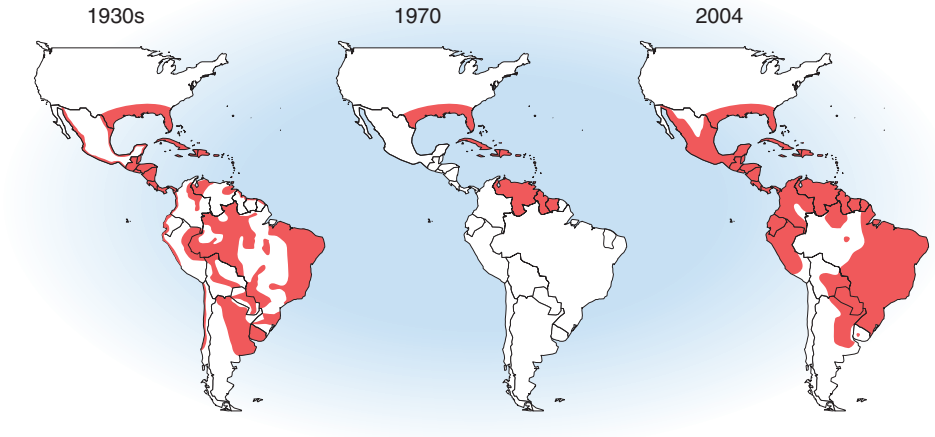

FIGURE 14-9 Geographic distribution of *Aedes aegypti* in the Americas in 1930, 1970, and 2004. *(From Gubler DJ. The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle?* Comp Immunol Microbiol Infect Dis. *2004;27:319-330.)*

of specific ecologic and behavioral factors that facilitate the introduction of animal pathogens into human populations (e.g., increased human presence or other changes in wildlife habitats) and allow newly introduced pathogens to become established in new areas (e.g., suitable insect vectors).[353]

Dengue

Dengue is the most important mosquito-borne viral disease that affects humans. Its global distribution is comparable to that of malaria, and an estimated 2.5 billion people live in areas at risk for epidemic transmission. The disease is endemic in Africa, the Americas, and parts of the Middle East, Asia, and the western Pacific. The frequency of dengue and its more severe complications—dengue hemorrhagic fever (DHF) and dengue shock syndrome—has been increasing dramatically since 1980.[354] It is generally estimated that 50 to 100 million infections occur annually, but recent data suggest that approximately 390 million dengue infections occurred worldwide in 2010, including 96 million symptomatic illnesses.[355] Dengue is caused by any of four antigenically distinct virus serotypes (DEN-1, -2, -3, -4) of the genus *Flavivirus.* Infection with one of these serotypes is not cross protective. Infection with dengue viruses produces a spectrum of clinical illness that ranges from a nonspecific viral syndrome to severe and fatal hemorrhagic disease.[356] DHF is a life-threatening condition characterized by capillary permeability that may lead to hypovolemic shock and death. Important risk factors for DHF include the strain and serotype of the infecting virus, as well as the age, immune status, and genetic predisposition of the patient. In endemic areas, most deaths from dengue infection occur in children younger than 15 years of age.[356] Economic impact analyses in both the Americas and Asia indicate that the burden of dengue-related illness in children is substantial, especially when nonhospitalized patients are considered.[357,358]

Dengue is transmitted primarily by *Aedes aegypti,* a domestic, daybiting mosquito, and secondarily by *A. albopictus. A. aegypti* was historically found in Africa but spread throughout the tropical regions of the world during the past 2 centuries through international commerce. It is well adapted to the urban environment, feeding on humans and breeding in containers in areas where water is stored or allowed to accumulate, such as discarded cans, bottles, plastic containers, and tires. Epidemics caused by multiple serotypes (hyperendemicity) have become more frequent, and the geographic distribution of both the viruses and their mosquito vectors has expanded.

The emergence of dengue and DHF in the Americas has been dramatic. In an effort to prevent urban yellow fever, which is also transmitted by *A. aegypti,* the Pan American Health Organization established a program in the 1950s and 1960s to eradicate the species from most of Central and South America.[353] As a result, epidemic dengue occurred only sporadically in some Caribbean islands during this period. The success of the program, however, led to its gradual discontinuation beginning in 1970. Since that time, *A. aegypti* has reestablished itself firmly in the region, now exceeding the extent of distribution that was seen before the eradication program began (Fig. 14-9). Epidemics of dengue fever now routinely occur in Venezuela, Colombia, Brazil, and other locations in Latin America and the Caribbean.[359] Puerto Rico, which has experienced epidemic dengue activity periodically since 1963, suffered the largest dengue outbreak in its history in 2010, affecting more than 21,000 people.[360] In 2009 and 2010, Florida reported the first cases of dengue acquired in the continental United States outside the Texas-Mexico border since 1945.[361] Multiple outbreaks in Africa were identified in 2013.[362] A number of lines of evidence suggest that dengue is endemic in Africa on a par with the Americas but is not well recognized.[355,363]

No therapy is effective for dengue infection, and treatment is supportive, with particular attention to fluid management.[354] In Puerto Rico, deaths from dengue were reduced by training physicians in early detection and appropriate supportive care of patients with dengue hemorrhagic fever.[364] A U.S. Food and Drug Administration (FDA)-approved, real-time polymerase chain reaction (RT-PCR) assay that can detect all four dengue serotypes in the first 7 days after symptom onset was developed by the CDC and is available from the agency at the time of this writing, although wider availability through commercial sources is desirable (www.cdc.gov/dengue/resources/rt_pcr/CDCPackageInsert.pdf28).

It has been a long-standing challenge to develop a safe dengue vaccine that is effective against all four serotypes, complicated by concerns that vaccination might predispose to the severe form of dengue infection and by the poor understanding of the immunologic correlates of immunity. However, there has been considerable progress in the recent past and a number of candidate dengue vaccines are currently being evaluated, including live attenuated, inactivated, chimeric, DNA, and viral-vector vaccines.[365] Results of a phase IIb trial of the vaccine candidate farthest along in clinical trials, a recombinant live-attenuated tetravalent vaccine manufactured by Sanofi Pasteur, showed that the vaccine was safe but the protective efficacy was only 30.2% with a confidence interval that included zero.[366] Several other candidate vaccines currently are in phase II trials.

Efforts to reverse the recent trend of increased epidemic activity and geographic expansion of dengue are not promising. New dengue virus strains and serotypes will likely continue to be introduced into many areas with high population levels of *A. aegypti.* In the absence of a vaccine or new mosquito control technology, public health authorities have emphasized disease prevention and mosquito control through community efforts to reduce larval breeding sources. Improved

laboratory-based surveillance systems and other innovative approaches that can provide early warning of a potential dengue epidemic are also needed to alert the public to take protective action and physicians to diagnose and properly treat cases.

Chikungunya

Chikungunya shares many similarities with dengue, both in terms of epidemiology and clinical illness. Like dengue virus, chikungunya virus is transmitted by *A. aegypti* and *Aedes albopictus* mosquitoes and is characterized by acute onset of fever, joint and muscle pain, headache, nausea, fatigue, and rash. Indeed, chikungunya is frequently misdiagnosed as dengue, and outbreaks of the two diseases can occur simultaneously.[367] Chikungunya is, however, caused by a member of the family Togaviridae, genus *Alphavirus.* Chikungunya virus infection is noteworthy in that joint pain is a prominent feature of the disease, a condition that may persist for months. Joints most commonly involved include ankle, knee, wrist, and small joints of the hands. Chikungunya was first detected in Tanzania in 1953 and spread to other parts of Africa and parts of Asia.[368,369]

Chikungunya virus is an important cause of febrile illness[370] in Africa and Asia, including the Indian subcontinent. Epidemic cycles occur with interepidemic periods ranging from 4 to 30 years.[371] Since 2004, chikungunya has caused large outbreaks in a wide range throughout Asia and Africa. In 2004, an outbreak was identified in Kenya, and subsequently outbreaks occurred in Indian Ocean islands and South India during 2005-2006.[367,369] These outbreaks were characterized by high clinically apparent attack rates and were noteworthy in that higher than expected crude death rates occurred among affected populations, especially among the oldest age groups.[372] From March 2005 through April 2006, an estimated 255,000 cases of chikungunya occurred in Réunion (population 770,000), and excess deaths were recorded, suggesting a case-fatality rate of approximately 1 in 1000, mainly in persons 75 years of age and older.[372] Similar elevated mortality rates were seen among the elderly in Mauritius during the 2006 outbreak.[373] In India, more than 1.25 million suspect chikungunya cases were reported from 151 districts in eight states in 2006, with attack rates reaching 45% in some communities.[367] Between July and September 2007, an outbreak of chikungunya occurred in northeastern Italy, the first chikungunya outbreak to occur in a temperate region. The index case was likely a traveler from India who developed symptoms while visiting relatives in the outbreak region. More than 200 suspected cases were reported between July and September 2007, and chikungunya virus sequences were detected in pools of *A. albopictus* mosquitoes by PCR assay.[374]

Humans infected with chikungunya virus have viremias of sufficient titers to infect feeding vector mosquitoes and are thus an ideal source for virus dissemination and introduction into new regions. In addition, one of the principal vectors, *A. albopictus,* has been introduced into many areas of Europe and North America, raising concern that temperate and tropical regions around the world may be receptive to future outbreaks of chikungunya.[375] Recent studies suggest that the virus is adapting to facilitate transmission by this species.[376] Preparedness and response strategies focus on early detection of cases, timely and appropriate epidemiologic investigation, and the institution of measures to mitigate spread.[371] The recognition of chikungunya as an emerging health threat has also stimulated innovative research on vaccine development[377-379] and on new antiviral therapies that involve viral or host targets.[380]

West Nile Virus

West Nile virus (WNV) is another example of a vector-borne pathogen that has spread rapidly into new areas. WNV was first isolated in 1937 from an apparently healthy individual from the West Nile district of Uganda.[381] For decades, WNV was recognized as an important endemic and occasionally epidemic disease in Africa and the Middle East, causing primarily minor febrile illness.[382] However, since 1998, major outbreaks associated with severe neurologic disease have occurred in Romania,[383] Russia,[384] Israel,[385] the United States,[386] and Canada.[387] The disease was first reported in North America in 1999 when the virus caused an outbreak of severe neuroinvasive disease that resulted in seven deaths in New York City.[386] Since then, WNV has spread across the continental United States, becoming endemic and the leading cause of arboviral disease in the country—affecting thousands of people each year.[388,389] By 2005 the virus had spread to an area extending from central Canada to southern Argentina.[390-392] WNV is recognized as the most widely distributed arbovirus in the world.[393] Major U.S. outbreaks occurred in 2002 (2945 cases of neuroinvasive disease and 284 deaths), in 2003 (2866 neuroinvasive disease cases and 264 deaths), and in 2012 (2873 neuroinvasive disease cases and 286 deaths).[394] Texas was at the epicenter of the 2012 outbreak,[395] reporting about one third of all cases. It is estimated that a cumulative 2 million to 4 million infections and 0.4 million to 1 million resulting illnesses occurred in the United States from 1999 to 2010.[389]

WNV is a single-stranded RNA virus of the Flaviviridae (genus *Flavivirus*), which is part of the Japanese encephalitis virus antigenic complex. In addition to Japanese encephalitis, this complex includes St. Louis encephalitis virus, Murray Valley encephalitis virus, and Kunjin virus, a subtype of WNV.[382] WNV is transmitted to humans primarily through the bite of infected mosquitoes, but person-to-person transmission can occur through transfusion of infected blood products or solid-organ transplantation.[396-398] Because the U.S. blood supply has been routinely screened for WNV RNA since 2003, transfusion-associated WNV infection is rare.

The virus is maintained in a bird-mosquito-bird cycle, with birds developing high levels of viremia and serving as amplifying hosts. Mosquitoes primarily of the genus *Culex* transmit WNV, although the virus has been isolated from many genera and species of mosquitoes. Although most species of infected birds generally remain asymptomatic, WNV-related mortality has been noted in more than 160 avian species in the United States and Canada.[399] Crows and related birds of the Corvidae are especially susceptible to mortality from WNV infection, and die-offs of these birds have been used as one indicator of active WNV transmission.[399] Equines are frequently infected with WNV, with 36 U.S. states reporting equine infections in 2009.[400]

Approximately 80% of WNV infections in humans are asymptomatic, 20% develop fever, and less than 1% are WNV neuroinvasive disease. Most symptomatic persons have an acute febrile illness consisting of headache, myalgia, or arthralgia that lasts from 3 to 6 days.[401] WNV neuroinvasive disease is characterized by acute neurologic manifestations, usually encephalitis, meningoencephalitis, or acute flaccid paralysis.[384,396,402] The mortality rate from WNV neuroinvasive disease is approximately 10%. Long-term outcome among survivors varies, with some persons showing little neurologic and functional improvement and others experiencing substantial gains.[403] Persons suffering paralytic disease with respiratory involvement are at greatest risk for death and have a poor long-term outcome.[401-403]

Although WNV strains circulating in the United States have genotypic differences and the predominant circulating strain has changed over time,[404,405] no strain-specific differences in virulence or clinical disease in humans have been documented, and no antigenic differences have been identified that would pose a challenge to vaccine development. Nevertheless, the sporadic and unpredictable pattern of WNV incidence represents a considerable barrier to randomized clinical trials of vaccines or treatments.[406] Although vaccines for use in horses are licensed—and phase I and II clinical trials of candidate vaccines for human use have been completed—no phase III trials in humans have been attempted.[407] At the present time, prevention of WNV infection relies on a cadre of efforts that include mosquito, bird, and human disease surveillance; mosquito control; the use of personal protective measures; and screening of the blood supply. There is no treatment of proven efficacy for WNV infection.[392]

Ebola and Marburg Hemorrhagic Fevers

Ebola and Marburg hemorrhagic fevers are severe, often-fatal diseases in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). Symptoms include fever, headache, joint and muscle aches, sore throat, and weakness, followed by diarrhea, vomiting, and stomach pain. Some patients also exhibit a rash, red eyes, hiccups, and internal and external bleeding. There is no vaccine or standard treatment for Ebola or Marburg. Supportive therapy involves balancing fluids and electrolytes, maintaining oxygen status and blood pressure, and providing treatment for any complicating infections.[408]

The causative agents of Ebola and Marburg hemorrhagic fevers are filoviruses, belonging to the Filoviridae. These viruses are associated with fruit bats, which may be their natural animal reservoirs.[409-412] Marburg virus was detected first, in 1967, when 31 cases (7 fatal) occurred in Germany and Yugoslavia among laboratory workers handling tissues from African green monkeys.[413] Eight years later, in 1975, a traveler returning from Rhodesia (now Zimbabwe) died in a hospital in Johannesburg, South Africa; his traveling companion and a nurse subsequently became ill, although both survived.[414] During the 1980s, two cases of Marburg hemorrhagic fever were reported in visitors to Kitum Cave in Mount Elgon National Park, Kenya.[415,416]

Ebola virus was first detected in 1976 as the cause of outbreaks with high fatality rates in Zaire (now the Democratic Republic of the Congo)[417] and the Sudan.[418] The Ebola strains associated with the 1976 outbreaks were named Ebola-Zaire and Ebola-Sudan. Other Ebola strains that cause human disease include Ebola-Ivory Coast (isolated in 1994 when a scientist became ill after conducting an autopsy on a chimpanzee from the Tai Forest)[419] and Ebola-Bundibugyo (isolated in 2007 during an outbreak in Uganda).[420] A case of Ebola-Sudan was reported in the United Kingdom in 1976 in a laboratory worker infected via the accidental stick of a contaminated needle,[421] and a case of Ebola-Zaire was reported in South Africa in 1996 in a physician who had traveled to Johannesburg after treating Ebola virus–infected patients in Gabon (the site of three Ebola outbreaks during the 1990s). The physician survived, but a nurse who took care of him became infected and died.[422] A fifth strain of Ebola was identified in Reston, Virginia, as the cause of severe illness and death in Philippine monkeys imported by research facilities in the United States in 1989 and 1990[423,424] and Italy in 1992.[425] In 2008, Ebola-Reston was detected in pigs on two farms in the Philippines.[426] Six workers from the pig farm and from a slaughterhouse developed antibodies but did not become ill.

Outbreaks of Ebola have recurred multiple times in central and East Africa over the past decade, in the Republic of the Congo in 2003,[427,428] in the Sudan in 2004,[429] in the Democratic Republic of the Congo in 2007,[410] 2008-2009,[430] and 2012,[345] and in Uganda in 2007-2008[420] and twice in 2012.[345,431] Outbreaks of Marburg occurred in the Democratic Republic of the Congo in 1998 to 2000 among workers at a gold mine,[432] in Angola in 2005,[433] and in Uganda in 2007[434] and 2012.[345,431] Although viral hemorrhagic fever outbreaks have lasted from a few months to more than a year, the Ebola and Marburg outbreaks that occurred in Uganda in 2012 were contained within 3 weeks. Hemorrhagic fever outbreaks typically result from a single or small number of spillover events from the virus reservoir with subsequent chains of human-to-human transmission in community (sometimes associated with funerals) and hospital settings.[435] Transmission in health care settings can be prevented by adherence to basic infection control practices and proper disposal of potentially infectious items.[436] The four distinct filovirus outbreaks that occurred in Uganda and the Democratic Republic of the Congo in 2012 were quickly identified and brought under control. That these outbreaks were kept relatively small is attributable in part to the availability of in-country filovirus diagnostics at the viral hemorrhagic fever reference laboratory located at the Uganda Viral Research Institute (UVRI) in Entebbe. This laboratory is a component of a viral hemorrhagic fever surveillance program established in 2010 by the UVRI and the Uganda Ministry of Health, in collaboration with the CDC.[345,431]

Current challenges include improving regional disease surveillance, developing additional diagnostic tools to assist in early diagnosis, and conducting ecologic investigations of Ebola and Marburg viruses. A better understanding of the natural reservoirs of these viruses and how they are spread may help prevent future outbreaks.

TICK-BORNE DISEASES

Public health concern about tick-borne diseases has increased in the United States, owing to the geographic spread of Lyme disease (along with its vector, the black-legged tick, *Ixodes scapularis*),[437-439] and the discovery of a new vector (the brown dog tick, *Rhipicephalus sanguineus*) for Rocky Mountain spotted fever, identified during the investigation of outbreaks in Arizona.[440] Moreover, two new tick-borne pathogens have been identified in the United States whose epidemiology and transmission patterns are the subject of ongoing study: an *Ehrlichia muris*–like agent in Minnesota and Wisconsin[441] and the Heartland virus in Missouri.[442] Based on small numbers of patients, the *Ehrlichia muris*–like agent appears to cause fever, malaise, fatigue, headache, nausea, and vomiting, whereas the Heartland virus is associated with a flulike illness, with fever, fatigue, loss of appetite, and diarrhea. Like the mosquito-borne Rift Valley fever virus, the Heartland virus is a phlebovirus, a genus of the Bunyaviridae family of negative-stranded, enveloped RNA viruses. It is the first tick-borne phlebovirus known to cause human disease in the Americas.

Another novel phlebovirus—also thought to be tick-borne—was recently reported in China as the cause of an outbreak of severe fever with thrombocytopenia syndrome, with a case-fatality rate of 12% (171 confirmed cases and 21 deaths).[443,444] The severe fever with thrombocytopenia syndrome virus, which can cause fever, vomiting, diarrhea, and multiple organ failure, may be transmitted to humans by *Haemaphysalis longicornis* ticks carried by domestic animals[443,444] and may also spread from person to person through direct contact with infected blood or mucus.[445-447]

ANTIMICROBIAL RESISTANCE

Although the introduction of antibiotics in the early to mid-20th century remains one of the most significant health achievements to date, antimicrobial resistance is regarded as one of the greatest threats to human health worldwide.[448-450,451,452,453] The widespread availability and use of antimicrobial agents among humans and animals, along with a globalized society in which emerging resistant strains can quickly spread worldwide, has created an environment of antibiotic exposure thus intensifying selective pressure and boosting the inherent capacity of microbes to develop resistance genes. Each year, antibiotic-resistant infections cost the U.S. health care system more than $20 billion and are responsible for more than 8 million additional hospital days.[454,455] Moreover, these infections often require the use of less effective, more expensive, and often more toxic drugs. Areas of particular concern include continued threats from multi- and pan-resistant strains of *Mycobacterium tuberculosis,* health care– and community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections with continued evolution and global spread of highly virulent clones, along with newer challenges including increases in highly resistant gram-negative bacteria, particularly carbapenem-resistant Enterobacteriaceae and increasing resistance to third-generation cephalosporins in persons infected with *Neisseria gonorrhoeae.*[456] Also of concern are increases in severe, life-threatening *C. difficile* infections, usually associated with recent antibiotic use and often occurring among hospitalized patients (see "Diarrheal Disease"). As conduit and amplifier of antimicrobial resistance, health care settings are critical to its control.

The evolving nature of microbes defines antimicrobial resistance. Resistance genes have been found in humans and animals in areas with limited to no antibiotic exposure, in bacterial DNA frozen in the Arctic for 30,000 years, and in bacteria from underground caves isolated for 4 million years, some of which were resistant to synthetic antibiotics developed in the 20th century.[457-459] Enhancing this evolutionary process is antibiotic exposure. After introduction of each new class of antibiotics has come global spread of resistant strains, with factors such as global travel and trade accelerating this spread (Fig. 14-10). As early as the 1930s, sulfonamide-resistant strains of *Streptococcus pyogenes* were noted in military hospitals, and numerous bacterial strains, including *S. aureus,* were found to be resistant to penicillin shortly after its introduction and use in the 1940s.[460,461] In 1961, just 2 years after the introduction of methicillin, MRSA strains emerged in British hospitals,[462,463] and strains exhibiting intermediate or high level resistance to vancomycin have been identified since 1996.[464,465,466,467]

Similar patterns of resistance have emerged in other important pathogens. For *N. gonorrhoeae,* resistance to sulfonamides was common by the 1940s, and penicillin- and tetracycline-resistant strains became widespread during the 1980s.[468] Fluoroquinolone-resistant strains emerged during the 1990s and 2000s and spread quickly, leaving cephalosporins as the only remaining antimicrobial agents for treatment of gonococcal infections.[469] In recent years, the emergence of strains with decreased susceptibility to cephalosporins has threatened a

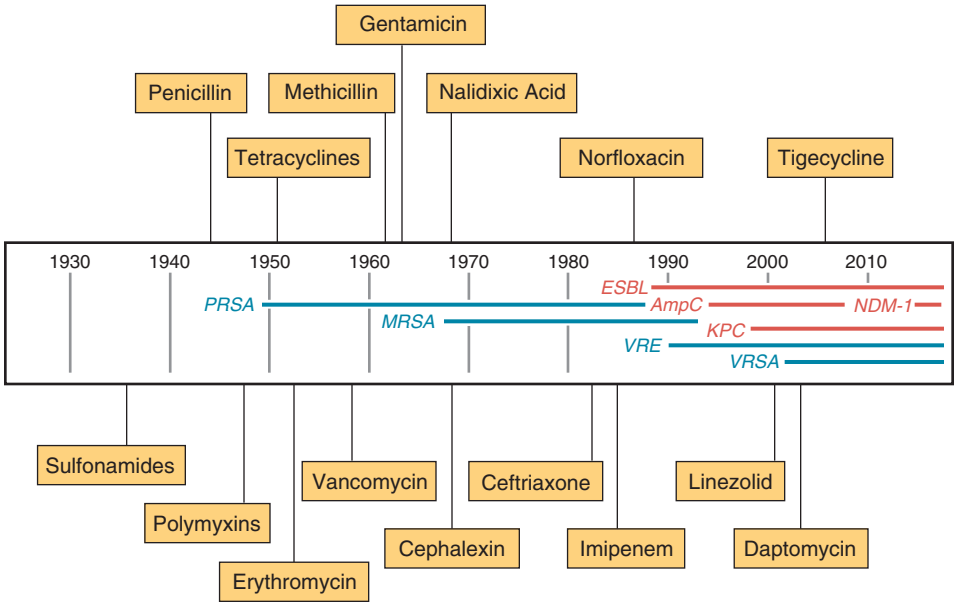

FIGURE 14-10 Antibiotic and resistance timeline. This timeline indicates the approximate dates that the major antibiotic classes or important antibiotics of each class were introduced into clinical use. The dates that resistant organisms were identified are shown in the center of the timeline. AmpC, AmpC-producing Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase–producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*; NDM-1, New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae; PRSA, penicillin-resistant *S. aureus*; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *S. aureus*. *(From Molton JS, Tambyah PA, Ang BS, et al. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia.* Clin Infect Dis. *2013;56: 1310-1318.)*

return to potentially untreatable gonorrhea and prompted changes in U.S. gonorrhea treatment guidelines to prolong the effectiveness of these drugs.[470,471] Over the past 2 decades, highly drug-resistant strains of *M. tuberculosis* have also emerged worldwide,[472] including multidrug-resistant tuberculosis (defined as tuberculosis that is resistant to isoniazid and rifampin, the two most effective first-line tuberculosis drugs) and extensively drug-resistant tuberculosis (defined as multidrug-resistant tuberculosis that is also resistant to any fluoroquinolone drug and at least one of three second-line injectable drugs: amikacin, kanamycin, or capreomycin). A survey of more than 25 international reference laboratories conducted by the WHO and CDC found that during 2000 to 2004, among 17,690 *M. tuberculosis* isolates, 20% were multidrug resistant and 2% were extensively drug resistant.[473] Although tuberculosis cases in the United States continue to decline, an estimated one third of the world's population is infected with *M. tuberculosis,* and each year approximately 9 million people develop tubercular disease and 2 million die from tuberculosis-related deaths.[474] These infections present serious public health challenges and raise the specter of virtually untreatable tuberculosis outbreaks.[475]

Carbapenem-resistant Enterobacteriaceae are also particularly alarming, with some showing resistance to all available antibiotics.[476,477] These infections are primarily transmitted in health care settings and can be severe, with mortality rates of 40% to 50%.[478-480] Patients who require prolonged hospitalization and critically ill patients exposed to invasive medical devices (e.g., ventilators and central venous catheters) are at special risk. Resistance to carbapenem antibiotics is mediated through the production of carbapenemases (enzymes that inactivate carbapenems), including *Klebsiella pneumoniae* carbapenemase (KPC), first identified in 2001 in the United States,[481] and New Delhi β-lactamase (NDM), first identified in 2008 in India.[482] The genes encoding KPC and NDM (carried on plasmids) have spread from *K. pneumoniae* to other gram-negative bacteria, including *E. coli, Klebsiella* species, and *Enterobacter* species.

The problem of antimicrobial resistance extends beyond bacteria and includes many priority viral (e.g., HIV, influenza), fungal (e.g., *Candida, Aspergillus*), and parasitic (e.g., malaria) infections. However, the increasing use of antibiotics in both humans and animals, the spread of HAIs into communities, and a virtual standstill in antibiotic development have escalated bacterial antibiotic resistance to crisis levels and garnered the attention of public health, clinical, and policy leaders worldwide.

Efforts to reduce antimicrobial resistance have largely focused on surveillance and infection control in health care settings, along with educational campaigns targeted to health care providers and consumers on judicious antimicrobial use, such as the CDC's "Get Smart: Know When Antibiotics Work" campaign.[483] In recent years, impressive gains have been made by U.S. health care settings in reducing several types of HAIs, many of which are drug resistant.[484] As an example, invasive hospital-acquired MRSA infections declined 28% from 2005 through 2008[485] and MRSA bloodstream infections in hospitals decreased nearly 50% between 1997 and 2007.[486] These and other declines in hospital-acquired infections followed targeted, multifaceted efforts undertaken to increase adherence to recommended infection control practices, educate patients and providers, issue facility-specific guidelines for prescription and use of antimicrobial agents, and implement appropriate isolation and cohorting of patients infected or colonized with drug-resistant organisms. In addition, hospital-acquired infections are reported and tracked by the Centers for Medicare and Medicaid Services (CMS) and through reporting mandates in many states using the CDC's National Healthcare Safety Network (NHSN). This secure, Internet-based surveillance system collects data from more than 12,000 facilities in all 50 states on hospital-acquired infections and related issues, including the incidence or prevalence of multidrug-resistant organisms, health care personnel safety and vaccination, and the occurrence of transfusion-related adverse events. Reviews of antibiotic stewardship programs in both large and small hospitals have documented their effectiveness, with facility-specific reductions in antibiotic use of 22% to 36% and related annual cost savings of $200,000 to $900,000.[487,488] With 50% of antibiotic prescriptions estimated to be unnecessary,[489] education of patients and providers on the importance of and health benefits from responsible use of antibiotics remains paramount.

Use of antibiotics as growth promoters in healthy food-producing animals is also a significant concern. Globally, the amount of antibiotics used in food-producing animals surpasses the amount of antibiotics used to treat human disease.[450] The human health implications of this

use are increasingly being recognized. A recent study comparing workers in industrial and antibiotic-free livestock operations found livestock-associated MRSA and multidrug-resistant *S. aureus* carriage only among the industrial workers.[490] Linkages have also been found between *E. coli* isolates from retail meat (chicken) and extraintestinal pathogenic *E. coli* urinary tract infections in humans, potentially affecting treatment of these common infections.[491] Several nations have taken steps to address the nontherapeutic use of antibiotics in food-producing animals, beginning with Sweden in 1986 and extending to the European Union in 2006, with bans on agricultural growth promoters.[492] The FDA strategy to promote the judicious use of antibiotics important in treating humans recommends that such antibiotics be used in food-producing animals only under veterinary oversight and only to address animal health needs, not to promote growth.[493]

For antimicrobial drug development, the outlook is grim. Despite the continued rise in antibiotic-resistant pathogens, the development of new antibiotics has dramatically slowed. For the 5-year period 1983 to 1987, 16 new systemic antibiotics were approved for use in humans by the FDA; from 2008 to 2012, only 2 were approved.[494] Particularly troubling, there have been no new classes of drugs to treat gram-negative bacteria in 4 decades.[488] With the discovery of new antimicrobial agents more scientifically challenging compared with earlier years, unfavorable profit margins from short-course therapies, and other disincentives, many pharmaceutical companies have abandoned the market. Several U.S. policy steps have been taken to counteract these effects, including the FDA Safety and Innovation Act,[495] passed into law in 2012, which seeks to increase the development of and patient access to new antimicrobial agents.

More recent efforts have focused on the use of new technologies and host targets to better understand and reduce antimicrobial resistance. Whole-genome sequencing techniques have been used to track bacterial transmission from person to person and to better define and determine transmission linkages in outbreaks of resistant HAIs.[496-498] As these technologies continue to advance, rapid, point-of-care diagnostic tests could be used to quickly identify resistant infections and target treatment. Efforts to prevent and control infectious diseases by altering the host-microbe interaction as opposed to targeting microbes (e.g., fecal transplants to treat *C. difficile*) also offer tremendous promise for reducing antimicrobial resistance.

Vaccines represent the optimal solution to addressing infections and antimicrobial resistance, and research and development of new vaccines is an urgent need. Effective immunization programs have stopped emergence of resistant strains and precluded the need for new antimicrobial agents for multiple infectious diseases, allowing focus to be shifted to diseases for which drug resistance remains a major global health threat. A recent example of this impact includes the pneumococcal conjugate vaccine. Over the past several years, use of this vaccine not only has reduced the rate of disease but also has decreased antibiotic resistance by targeting pneumococcal strains that are most often resistant.[499-501]

CONTROLLING THE THREATS

The cross-border spread of infectious diseases, the upsurge in newly identified infections along with the emergence of known infections in new geographic regions, the unrelenting evolution of resistant organisms, and continued concerns about bioterrorism serve as compelling reminders of the importance of ensuring strong and sustainable clinical, public health, and laboratory capacity and collaborations at the local, national, and international levels.[502] These fundamental elements can help create globally linked surveillance and laboratory systems that can facilitate rapid recognition of and response to infectious disease events.[503,504]

The World Health Organization has long played a major role in establishing and supporting such global health collaborations. A primary example is the Global Influenza Surveillance and Response System (GISRS) (Fig. 14-11), in operation for more than 6 decades.[505] Formerly known as the Global Influenza Surveillance Network, GISRS currently comprises six WHO collaborating centers, four WHO Essential Regulatory Laboratories, and 141 institutions across 111 countries (WHO member states). Responsibilities include monitoring the evolution of influenza viruses and providing recommendations on laboratory diagnostics, vaccine development, and risk assessment. Also critical is WHO's Global Outbreak Alert and Response Network (GOARN),[506] a collaboration of existing networks and institutions

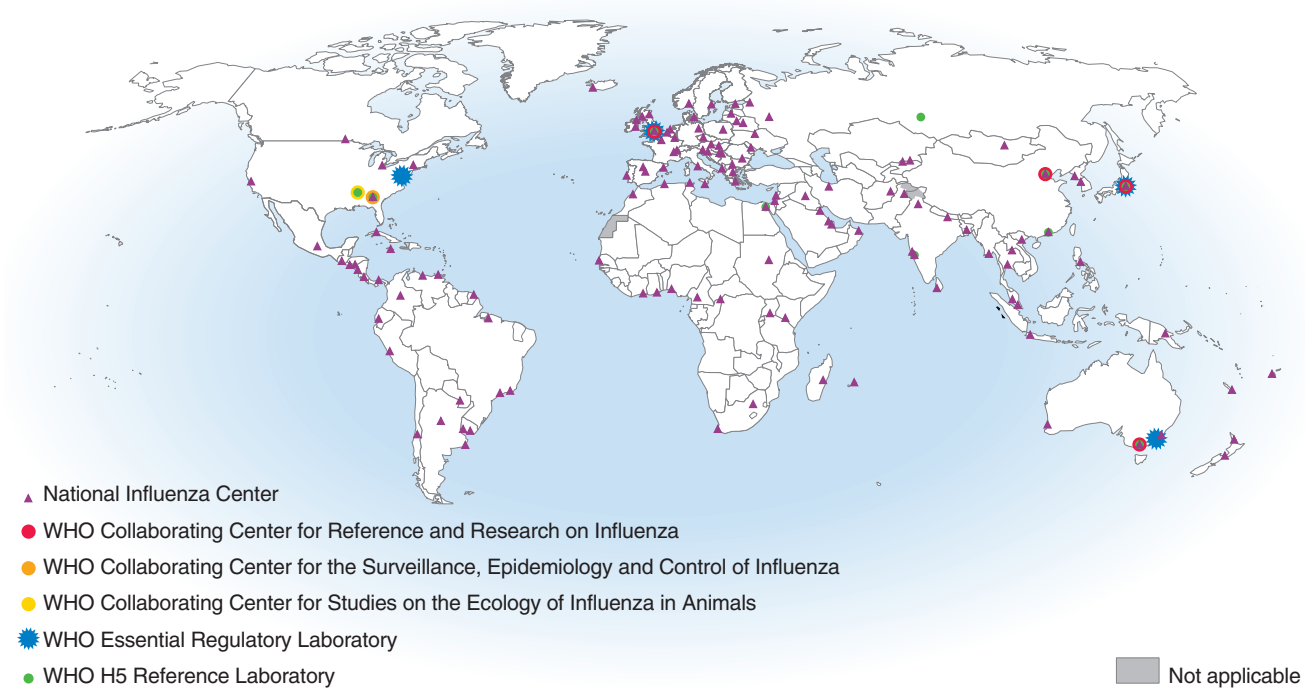

FIGURE 14-11 WHO Global Influenza Surveillance and Response System. *(From World Health Organization [http://www.who.int/influenza/gisrs_laboratory/en/]. Available at* http://www.who.int/whr/2007/media_centre/07_chap2_fig02_en.pdf.*)*

established in 2000 to address threats from epidemic-prone and emerging infectious threats. GOARN provides an operational framework to ensure the availability of skills, expertise, and resources needed to keep the international community aware of and ready to respond to potential outbreaks.[507]

In the aftermath of the 2003 SARS outbreak, the global public health community completed work on new International Health Regulations (IHR), an international treaty that gives the WHO authority over and places requirements on its member states for detecting, reporting, and controlling infectious diseases.[508] Adopted by the World Health Assembly in 2005 and made effective in 2007, the new regulations require prompt reporting of all public health emergencies of international concern, expanding beyond infectious diseases to include events resulting from biological, chemical, or radionuclear threats as well as natural disasters. In addition to reporting of public health emergencies of international concern, the regulations require member states to notify the WHO of a single case of smallpox; poliomyelitis due to wild-type poliovirus; SARS; and human influenza caused by a new subtype. With the goal of controlling health threats at the local level, the new regulations allow for the use of surveillance information beyond official state notification and have established new requirements for member states to support existing global surveillance and response systems and to develop proactive systems for strengthening national and international capacities.

Significant contributions to global health and infectious disease control have also been made through private-sector support. A leading example is the Bill and Melinda Gates Foundation (www.gatesfoundation.org), a privately funded effort begun in 2000 focused on reducing health disparities across the world and helping to address the global health challenges outlined by the 2000 Millennium Development Goals (www.un.org/millenniumgoals). Priorities for the Gates Foundation include efforts to reduce HIV infection/AIDS, malaria, tuberculosis, vaccine-preventable diseases, diarrheal diseases, pneumonia, and neglected infectious diseases. Other important global health initiatives supported by both government and nongovernment donors include the Global Alliance for Vaccines and Immunizations (GAVI Alliance; www.gavialliance.org) and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (www.theglobalfund.org). Two large U.S.-led efforts, the President's Malaria Initiative (PMI; www.fightingmalaria.gov) and the President's Emergency Plan for AIDS Relief (PEPFAR; www.pepfar.gov) provide targeted prevention and treatment support in countries most heavily affected by these leading killers. In particular, the impact of PEPFAR has been dramatic. Begun in 2004, the program requires country ownership and results-based efforts with goals for sustainability. In 2011 alone, PEPFAR supported treatment of nearly 4 million people, supported antiretroviral therapy for more than 1.5 HIV-infected pregnant women to prevent perinatal infection, and supported diagnostic testing for more than 40 million individuals.[509]

Although national and global partnerships are critical to controlling infectious disease threats, local clinical, public health, and laboratory capacity remains the cornerstone for initial disease recognition and response. In the early 1980s, concerns by staff in the CDC's parasitic disease drug service regarding requests from physicians in New York and California for pentamidine isethionate for treatment of *Pneumocystis carinii* (now *Pneumocystis jirovecii*) pneumonia in patients with no known cause of immunodeficiency hinted at the first U.S. cases of AIDS.[510] Recognition of unusually severe respiratory disease by observant clinicians signaled hantavirus pulmonary syndrome in 1993, and suspicion of anthrax by alert clinical and laboratory staff in Florida in 2001 suggested a possible bioterrorist event. A February 10, 2003, email posted by a physician on ProMED, an informal online infectious disease reporting program of the International Society for Infectious Diseases, is widely regarded as the first notification of the global outbreak of SARS.[511] Such observations have not been limited to the medical and scientific community, however. In the mid-1970s, two Connecticut mothers questioning what was believed to be an unusually large number of juvenile rheumatoid arthritis cases in their community led researchers to the discovery of Lyme disease and a concerned American Legion official provided the first indication to health authorities of the emergence of legionnaires' disease.[512]

Although today's globalized world has created a perfect environment for rapid emergence and spread of infectious diseases, it has also brought significant scientific, technologic, and communication advances for their control. Next-generation sequencing technologies and expanded bioinformatics capacities are revolutionizing the field of microbiology, reducing the amount of time needed for pathogen detection and analysis and generating data for a more detailed understanding of infectious agents.[503,513] These tools offer new opportunities to improve public health efforts to detect and control outbreaks, determine antimicrobial susceptibility, and develop and target vaccines.[313,314,497,498] Scientists are also gaining new understanding of the role of the microbiome and microbial sensors in infectious diseases,[514,515] offering new insight into pathogen-host complexities and disease treatment and prevention. Continued advances in electronic communications are facilitating earlier recognition of emerging problems and rapid exchange of information. In particular, early warning systems such as ProMED-mail, the Public Health Agency of Canada's Global Public Health Intelligence Network (GPHIN), and HealthMap, collect, categorize, and display outbreak and disease information from a variety of formal and informal sources—enhancing disease surveillance and tracking capabilities.[516-518] Expansions in Internet access and use and far-reaching social media networks have also increased the exchange of health information and broadened public health partnerships to include nontraditional partners such as law enforcement, the media, and members of the public at local, national, and global levels.

Whereas focus on emerging and reemerging infections is paramount, requiring ongoing vigilance and a globally linked infrastructure, priority attention must remain on reducing high-burden infections that account for the majority of disease and disability caused by microbial agents.[5,6] These efforts should ideally work in tandem, enabling rapid recognition and effective response to emerging infections and other public health emergencies along with implementation of new and proven measures to reduce the burden of endemic infectious diseases and advance global health equity.

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