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## CHAPTER 5

# Category C Diseases and Agents

*Where the telescope ends, the microscope begins. Which of the two has the grander view?*

**Victor Hugo**

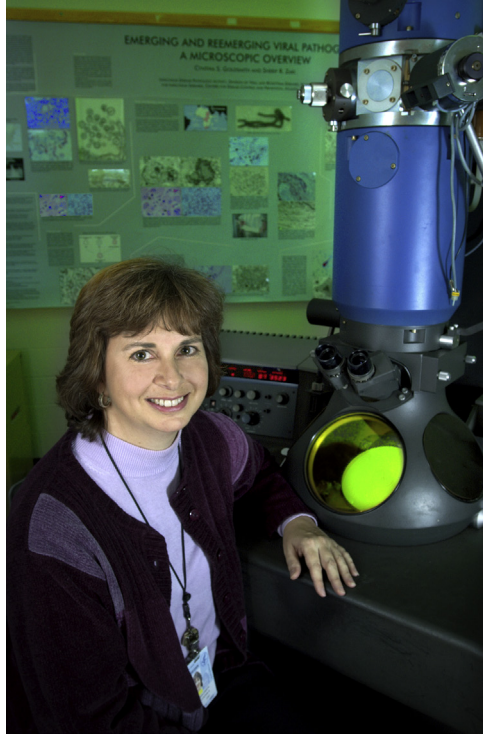
### Objectives

The study of this chapter will enable you to:

1. Discuss the importance of the Department of Health and Human Services (HHS) Category C agents.
2. List the most important pathogens currently found on the HHS Category C list.
3. Discuss the recent history of Nipah virus, hantavirus, West Nile fever virus, and the coronaviruses that are the causes of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).
4. Discuss the clinical symptoms, diagnostics, and treatments for Nipah virus fever, hantavirus, West Nile fever, SARS, and MERS.
5. Understand the challenges that public health officials and emergency management practitioners might face when an intentional release of a Category C agent occurs in their community.

### INTRODUCTION

Category C comprises newly **emerging diseases** and pathogens. No disease outbreak or epidemic escapes media coverage, whether it is an enteric disease due to contaminated lettuce, foodborne botulism, or the threat of “bird flu.” As Laurie Garrett points out in her thought-provoking book *The Coming Plague* (1995), we seem to be living in a world that is out of balance. Our era may very well be characterized by eruptions of new diseases, epidemics of old diseases moving into new areas, diseases that are sparked by advances in technology, and diseases that come to us from insects and animals as civilization invades ecologies where humans have not trodden before (Garrett, 1995). Although these encounters have been occurring throughout history, technology now enables us to define the problems with great acuity. Our ability to determine the causal relationship among pathogen, host, and disease relies heavily on state-of-the-art technologies brought to us by advances in science and engineering. Still, to this day the microscope remains a primary tool in the toolbox. Moreover, electron microscopy provides researchers with high-powered visual proof of the existence of the pathogens that cause disease (Fig. 5.1).



**Figure 5.1** Cynthia Goldsmith, a Centers for Disease Control (CDC) research biologist, seated in front of a transmission electron microscope. During the last 20 years at the CDC, Ms. Goldsmith's work as an electron microscopist has repeatedly played a key role in the rapid identification of emerging pathogens, including hantavirus, Nipah virus, and severe acute respiratory syndrome coronavirus. *Courtesy of US Health and Human Services, Public Health Image Library.*

The Category C list changes with the world disease outbreak situation. Bioterrorism coordinators, emergency managers, and public health officials should periodically check the Centers for Disease Control (CDC) website for updates. Consider how much attention has been brought to the emergence and spread of the deadly H5N1 influenza virus, also known as *bird flu*. In the last 12 years there have been a little more than 800 confirmed cases of H5N1 bird flu in humans. However, more than 50% of those human cases resulted in death and approximately 400 million birds have died either directly from the illness or indirectly from the control efforts aimed at eliminating the problem. Public health officials fear that H5N1 may spark the next pandemic. Bird flu due to the H5N1 virus is covered in Chapters [Biological Threat to Agriculture](#) and [Recent Animal Disease Outbreaks and Lessons Learned](#) because of the effect that this outbreak has had on the poultry industry.

Refer to [Table 5.1](#) for a snapshot of the Category C pathogens that have the attention of public health officials in 2015. A would-be terrorist or rogue state might take

**Table 5.1** Pathogens comprising Category C in July 2015

Pathogen, disease, or concern	Zoonoses	Primary means of transmission to humans
Nipah and Hendra viruses	Yes	Person to person
Tickborne hemorrhagic fever viruses	Yes	Tick bite
Yellow fever virus	Yes	Mosquito bite
Tuberculosis, including drug-resistant tuberculosis	No	Person to person
Avian influenza viruses	Yes	Person to person
Rabies virus	Yes	Animal bite
Prions	Yes	Ingestion
Chikungunya virus	Yes	Mosquito bite
Coccidioides species	No	Inhalation
Severe acute respiratory syndrome (SARS)	No	Person to person
Middle East respiratory syndrome coronavirus (MERS-CoV)	No	Person to person

Many of these are zoonotic, but the primary means of transmission of the agents varies widely from vector borne to person to person and event inhalation and ingestion.

advantage of any emerging pathogen or situation to create added fear, panic, and social disruption. The potential exploitation of an emerging pathogen is the reason why Category C exists. This Chapter explores four examples of emerging disease pathogens that have occurred in the past 20 years: Nipah virus, hantavirus, West Nile virus (WNV), severe acute respiratory syndrome (SARS) virus, and Middle East respiratory syndrome (MERS) coronavirus.

## NIPAH VIRUS

In 1998 a mysterious outbreak in the peninsular region of Malaysia caught public health officials by surprise ([Centers for Disease Control and Prevention, 1999](#)). The outbreak took place over an 8-month period. When it was over, more than 1 million pigs had to be destroyed. Moreover, there were 257 human cases from the same pathogen, which caused 105 deaths (a 41% case-fatality rate). Most human cases were from people employed in the swine industry who had direct contact with live pigs ([Parashar et al., 2000](#)). The outbreak had a profound psychological and economic impact on the country.

The outbreak was due to Nipah virus, a pathogen completely unknown to scientists before this outbreak (see [Fig. 5.2](#)). The pathogen was fully characterized by molecular methods as a paramyxovirus in the genus *Henipavirus* ([Wong et al., 2002](#)). Nipah virus is very similar to another recently emergent pathogen, Hendra virus, which causes severe respiratory and encephalitic disease in horses and humans.



**Figure 5.2** Under a highly magnified view of 168,000 $\times$ , this transmission electron micrographic image revealed ultrastructural details of a Nipah virus nucleocapsid, a virus named for the location in Malaysia where it was first isolated. *Courtesy of US Health and Human Services, Public Health Image Library.*

Nipah virus causes severe, rapidly progressive encephalitis in humans. In pigs, Nipah virus causes severe respiratory illness with neurological complications. Transmission of the virus to humans is associated with close contact with infected pigs. The survivability of Nipah virus outside of the host has not been determined.

In September 1998 the Malaysian Ministry of Health (MOH) began to receive reports from three geographic locations of several human cases of febrile encephalitis with high mortality. MOH authorities initially believed the outbreak was due to Japanese encephalitis (JE) virus, a mosquito-borne ribonucleic acid (RNA) virus. However, JE vaccination and mosquito control efforts conducted over several months failed to halt the epidemic. Numerous features of this outbreak's epidemiology were inconsistent with past JE outbreaks. Remarkably, researchers noted that human case patients had an association with infected animals from a concurrent and severe outbreak of respiratory disease in pigs and that there was a notable absence of illness in children. Subsequently, serological testing coupled with epidemiological findings showed that the Malaysians were not dealing with JE. Tissue culture isolation eventually led them to the actual etiologic agent of the outbreak (Chua et al., 1999). Nipah virus gets its name from the

village (Sungai Nipah) where the first cases were reported. In March 1999 a related outbreak occurred in Singapore, where abattoir workers were exposed to swine imported from Malaysia. The outbreak was quickly identified and stamped out.

## Transmission

The natural cycle of transmission of Nipah virus involves flying foxes (fruit bats, *Pteropus*) as reservoirs and pigs as amplifying hosts (Calisher et al., 2006). Hendra virus also is found in fruit bats. Many species of fruit bats are found in Malaysia. Two species of flying fox, the island flying fox (*Pteropus hypomelanus*) and Malayan flying fox (*Pteropus vampyrus*), have been shown to be asymptomatic carriers of the virus. No secondary hosts have been implicated.

Researchers have not yet determined how Nipah virus is transmitted from bats to pigs. They suspect that fruit trees close to pig pens are foraged by the bats and the virus is spread by this close proximity (urine or saliva on partially eaten fruit). Most human cases (93%) had direct contact with pigs or secondary contact with body fluids, urine, or feces (Calisher et al., 2006). Person-to-person transmission has not been established or related to any cases from the 1998–99 outbreak.

In the Malaysian outbreak of Nipah virus, the contagion was rapidly spread from farm to farm by the movement of infected pigs. Malaysia's domestic pig population before the outbreak was 2.4 million. The total annual value was estimated to be approximately \$400 million, with a total export value of \$100 million (US dollars). As a result of the outbreak, approximately 1.1 million pigs were culled to prevent the spread of the disease. This alone resulted in an estimated loss of \$217 million. During the outbreak, pork consumption in Malaysia dropped by almost 80% (Food and Agriculture Organization of the United Nations, 2002).

In 2004 an outbreak of Nipah virus occurred in Bangladesh. Only 34 human cases were identified; however, more than 75% of the case patients died (Hsu et al., 2004). Another outbreak of Nipah virus occurred in early 2005 in the Tangail District of Bangladesh, when 13 people became ill and lost consciousness after drinking palm fruit juice. The fruit may have been contaminated with infected fruit bat droppings. Blood samples from case patients were sent to the CDC to confirm Nipah virus infection; one was confirmed positive (Luby et al., 2006).

## Clinical Presentation, Diagnosis, and Treatment

The incubation period for Nipah virus in humans is believed to be 3–14 days. Initial symptoms are fever and headache. Nipah virus produces widespread effects and induces necrosis of endothelial cells in vasculature and neuronal damages. Subsequently, case patients experience dizziness, drowsiness, disorientation, and vomiting. Endothelial cells are involved in vascular permeability, and damage to the cells leads to vessel leaking and ultimately to hypovolemic shock. The most severely affected develop encephalitis,



seizures, and coma. Complications noted during the Malaysian outbreak included septicemia, intestinal bleeding, and renal impairment (Wong et al., 2002).

Laboratory diagnostic methods for Nipah virus infections now include serology, histopathology, immunohistochemistry, real-time polymerase chain reaction (PCR), and virus isolation. The virus is classified biosafety level (BSL)-4. There is no cure for Nipah; however, a vaccine is in development. Current treatment involves supportive care.

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### Nipah Virus and Biowarfare

Nipah virus has been listed by the CDC as a Category C potential bioterrorist agent. This is described as an emerging pathogen that has a potentially high morbidity and mortality as well as a major health impact. Currently, spread of the disease involves close contact with pigs. However, aerosolization may be a possible bioterrorist method of dispersal. In addition, the potential for this virus to infect a wide range of hosts and produce significant mortality in humans makes this emerging virus one of public health concern. Because of the need to cull infected pigs, attack with this agent could produce a great economic impact to a nation's pork industry. During the Nipah outbreak in Malaysia, widespread panic and fear occurred until the outbreak was brought under control.

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## HANTAVIRUS

An outbreak of a cluster of serious febrile illness occurred in New Mexico in 1993. A task force of scientists, public health experts, and epidemiologists discovered that the outbreak was due to hantavirus. **Hantavirus** is the causative agent of hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS) in humans (Duchin et al., 1994). From what we know now, this disease agent occurs naturally throughout most of North and South America, it is airborne, and in the absence of prompt medical attention infections are usually fatal. This agent serves as a perfect example of a pathogen that makes a dramatic entry into modern-day society, bringing with it numerous challenges. For its attributes and its sudden arrival, hantaviruses were placed in Department of Health and Human Services Category C.

Hantavirus is a three-segmented RNA virus in the family Bunyaviridae. Several rodent species act as the reservoir for these viruses in nature. Rodents transmit the disease horizontally within their species and vertically to humans through aerosolized virus particles from their dried feces and urine (LeDuc et al., 1992). The hantavirus-caused diseases HFRS and HPS are considered to be pan-American zoonoses. More than 25 antigenically different viral species make up this group. Table 5.2 provides a breakdown of hantavirus by type, endemic region, and rodent host.

Hantaviruses are encapsulated in a lipid envelope; therefore they are easily destroyed by common disinfectants, such as acetone, iodine, ethanol, and chlorine (Kraus et al., 2005). In addition, hantaviruses are deactivated by ultraviolet light, low pH, and temperatures above 37°C (98.6°F).

**Table 5.2** Hantavirus by type, endemic region, and host species

Hantavirus type	Endemic region	Rodent host species
Andes	Argentina/Chile	<i>Oligoryzomys longicaudatus</i> (long-tailed pygmy rice rat)
Bayou	Southeast United States	<i>Oryzomys palustris</i> (rice rat)
Black Creek Canal	Southeast United States	<i>Sigmodon hispidus</i> (cotton rat)
Dobrava	Europe, Balkans	<i>Apodemus agrarius</i> , <i>Apodemus flavicollis</i> (yellow neck mouse)
Hantaan	Asia, Far East Russia	<i>Apodemus agrarius</i> (striped field mouse)
Hu39694	Central Argentina	Unknown
Juquitiba	Brazil	Unknown
Laguna Negra	Paraguay/Bolivia	<i>Calomys laucha</i>
Lechiguanas	Central Argentina	<i>Oligoryzomys flavescens</i>
Monongahela	Eastern United States, Canada	<i>Peromyscus maniculatus</i> (deer mouse)
New York	Eastern United States, Canada	<i>Peromyscus leucopus</i> (white-footed mouse)
Oran	Northwest Argentina	<i>Oligoryzomys longicaudatus</i>
Puumala	Europe	<i>Clethrionomys glareolus</i> (red bank vole)
Seoul	Worldwide	<i>Rattus norvegicus</i> , <i>Rattus rattus</i> (Norway brown rat, roof rat)
Sin Nombre	Central and Western United States, Canada	<i>Peromyscus maniculatus</i> (deer mouse)

Hantaviruses previously recognized as causing HFRS in the Old World are Dobrava, Hantaan, Puumala, and Seoul. Infected rodents remain so for life, yet they are often unaffected by the virus and will transmit it among themselves. It is unknown whether animals other than the natural rodent hosts are epidemiologically important. Many other hantaviruses have been isolated and characterized but not linked to human illness. Most human infections with hantavirus in North America are associated with rodents of the subfamily *Sigmodontinae* (Childs et al., 1994). As many as three hantaviruses have been found circulating in one location, each with its own rodent reservoir. Rodents other than the primary reservoirs may play an important role as a carrier (a common reservoir for hantavirus is shown in Fig. 5.3).

## History

Disease outbreaks that occurred during the American Civil War are now believed to have been due to hantavirus. In addition, there are records of HFRS from both World Wars. What is thought to be the first outbreak of hantavirus causing HFRS was recorded in Russia in 1913. It is reported that Japanese troops in Manchuria experienced cases in 1932. In the early 1950s Western physicians recorded more than 3200 cases of an acute, debilitating, febrile illness in UN forces fighting in the Korean War. The illness, known as Korean hemorrhagic fever, affected soldiers living out of foxholes along the contested





**Figure 5.3** This is a cotton rat, *Sigmodon hispidus*, the habitat of which includes the southeastern United States and Central and South America. The cotton rat is a hantavirus carrier that becomes a threat when it enters human habitation in rural and suburban areas. Hantavirus is a deadly disease transmitted by infected rodents through urine, droppings, or saliva. Humans can contract the disease when they breathe in aerosolized virus. All hantaviruses known to cause hantavirus pulmonary syndrome are carried by New World rats and mice of the family Muridae, subfamily Sigmodontinae, which contains at least 430 species that are widespread throughout North and South America. *Courtesy of US Health and Human Services, Public Health Image Library.*

border between North and South Korea (Ricketts, 1954). Because the mortality rate was high (10–15%), the US Army Medical Department formed the Hemorrhagic Fever Commission to conduct an epidemiological investigation. Results of the commission indicated that a field mouse (*Apodemus agrarius coreae*) was harboring the infectious agent. However, it was not until 1977 that the infectious agent was isolated and named *Hantaan* for the river that runs near the 38th parallel, which separates North and South Korea (Lee et al., 2004). The Hemorrhagic Fever Commission preserved more than 600 serum samples from 245 soldiers. Later, in 1990, the serum samples from these 245 soldiers were screened for antibody to the Hantaan virus. Almost 40 years after the outbreak, investigators detected an antibody to Hantaan virus in 94% of the samples. In 1979 a virus similar to Hantaan caused hemorrhagic fever in laboratory workers. This virus, named Seoul virus after the site of the initial studies, infected Norway rats and roof rats shipped to Japan and Europe. Shipping these laboratory animals led to the dissemination of the Seoul virus.

### Four Corners Outbreak

In 1993 an outbreak of illness resulted in several fatalities on the Navajo Nation Indian Reservation in New Mexico. As the outbreak spread, cases were distributed around the

Four Corners region of the United States ([Chapman and Khabbaz, 1994](#)). The region gets its name from the perfectly formed grid square that marks the boundaries among the states of Arizona, Colorado, New Mexico, and Utah. These cases, later described as HPS, were attributed to a new species of hantavirus. Actually, nothing was new about it. The virus had probably been in the region for many years but had not been the cause of so much notable human illness in the past.

Several young Navajo tribal members presented to the Indian Health Service physicians with sudden onset of respiratory failure in May 1993. By June of that year, 12 people had succumbed to the illness. The illness was initially diagnosed as unexplained acute respiratory distress syndrome. Patients presented with abrupt fever, severe headache, myalgia, and cough followed by rapidly progressive pulmonary edema ([Stelzel, 1996](#)). Within 2–10 days, this condition led to respiratory failure, hypotension, and death. New Mexico Public Health officials teamed with CDC investigators to set up surveillance and laboratory testing. The team found that serum from the patients showed cross-reactive antibodies to Hantaan, Seoul, and Puumala virus antigens. However, the condition in these patients had developed into a pulmonary form unlike any other clinical presentation of hantavirus infection. The investigation also focused on the wildlife and domestic animals in the area of the outbreak ([Calisher et al., 1999](#)). Epidemiologists were quick to discover that the virus was being spread through the dried feces and urine of *Peromyscus* mice. Unfortunately, the Navajo believe that mice are responsible for bringing seeds to the earth, which enables humans to survive. The fact that mice are highly respected in Navajo culture made disease control efforts difficult. Tribal members had to accept all forms of rodent population management efforts, which include trapping, housecleaning, and reduction of harborage.

Outbreaks of hantavirus-related diseases are often attributed to weather patterns. Drought causes plants to die, which leads to a decrease in rodent populations. Conversely, heavy snowfall and spring rains allow plants to flourish and rodent populations to surge. These surges in the rodent population cause rodents to compete for food and protection in the dryer months that follow. The competition puts pressure on some infected rodents, forcing them into peridomestic environments, putting more people at risk for infection. HPS is most common in spring and summer months, when rodents are most active. Although the overall risk for HPS in endemic areas is relatively low, infections are associated with an increased population of rodents in and around the house. Activities that put people in contact with rodent droppings, urine, or nesting materials place the individual at higher risk for infection. Indoor exposures have been linked to rodents in the home or near dwellings, especially in colder months. Cleaning buildings that have been closed up for a period of time, such as cabins, barns, and storage facilities, also increases the risk of exposure.

Persons living in squalid housing conditions, those employed in agriculture, and those participating in wilderness camping or other outdoor activity in endemic areas are

at greater risk for hantavirus infections. Hikers and campers may be exposed when they use infested trail shelters or camp near rodent harborage. Construction and utility workers can be exposed when they work in crawl spaces under houses that may have a rodent population. Research shows that many HPS case patients acquired the virus after having been in frequent contact with rodents or their droppings for long periods ([Centers for Disease Control and Prevention, Special Pathogens Branch, 2007](#)).

Worldwide, approximately 150,000 hospitalizations due to HFRS are reported each year. Most cases come from China, where hantavirus was first recognized in 1931. Approximately 500 cases of Korean hemorrhagic fever are reported annually from South Korea. Many HFRS outbreaks occurring in Asia and Europe are due to people planting and harvesting crops having contact with field rodents.

## Transmission

Normally, humans become infected with hantavirus by the inhalation of aerosolized virus particles from rodent excreta. Transmission of hantavirus begins with a chronically infected rodent. Horizontal transmission occurs between rodents of the same species. Infections in rodents are asymptomatic and not deleterious to the rodent, making them ideal reservoirs. Rodents shed the virus in their urine, feces, and saliva. Humans become infected when they disturb the infected rodent's environment and breathe the infected particles, a process called *aerosolization*. Although less likely, transmission may occur through breaks in the skin. Virus particles may contaminate food sources and people may become infected through consumption. Very rarely, a bite from an infected rodent may cause disease. Person-to-person transmission of hantaviruses have not been reported. Several laboratory-acquired cases of HFRS have been reported. Hantaviruses are categorized as BSL-4 agents when propagating them in culture or passing them through laboratory animals known to be efficient reservoirs.

## Clinical Presentation, Diagnosis, and Treatment

The incubation period for hantavirus infection is believed to be 14–17 days. Initially, HPS case patients experience headache, fatigue, fever, increased respiratory and heart rates, and myalgia of the large muscles in the thighs, hips, back, and shoulders. Approximately half of all patients experience dizziness, chills, and various gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and abdominal pain.

Four to ten days after the initial presentation, patients begin to experience coughing, rales, and shortness of breath due to severe hypotension and rapidly progressive pulmonary edema, requiring immediate hospitalization and ventilation. Approximately 40% of HPS case patients die within the first 48 h because of hypoxia and shock.

The CDC maintains a national surveillance program for HPS. To assist physicians with the recognition of this illness, a specific case definition for HPS was published: a previously healthy person presenting with a febrile illness with a temperature at or above 101°F (38.3°C), unexplained acute respiratory distress syndrome, radiographic evidence

of bilateral interstitial infiltrate that develops within 1 week of hospitalization, and respiratory compromise that requires supplemental oxygen. If sudden death occurs before supplemental oxygen and noncardiogenic pulmonary edema is present on autopsy without an identifiable, specific cause of death, then diagnosis can be made ([Centers for Disease Control and Prevention, 1997](#)).

Confirmatory diagnosis of HPS requires meeting specific inclusion and exclusion criteria plus laboratory confirmation. The CDC uses enzyme-linked immunoabsorbent assay to detect the presence of hantavirus-specific immunoglobulin (Ig) M in acute-phase serum or a 4-fold increase in titers of IgG from acute- and convalescent-phase sera. Immunohistochemistry can be used on formalin-fixed tissues to detect hantavirus antigen when serum is unavailable. Virus detection by PCR or isolation from whole blood or serum may also be useful.

Treatment of HPS requires early and aggressive intensive care, focusing on oxygenation of the blood, electrolyte balance, and maintaining blood pressure. There was a grave prognosis for many of the initial victims of the Four Corners outbreak because health-care providers did not know what they were dealing with. Now, history of exposure leads physicians in endemic areas to a more rapid diagnosis. Early aggressive supportive care is needed for a successful resolution of symptoms. Without treatment, the prognosis for HPS is grave. With supportive care and symptom-targeted therapy, patients can recover from the disease. Chronic lung and heart damage may result depending on the aggressiveness of supportive care.

## WEST NILE VIRUS

WNV is a single-stranded RNA virus in the genus *Flavivirus* (family *Flaviviridae*). WNV is a member of the JE virus antigenic complex of mosquito-borne flaviviruses. Also included in this complex are Saint Louis encephalitis virus, Kunjin virus, and Murray Valley encephalitis virus.

WNV was initially isolated in 1937 from a febrile patient in the West Nile district of Uganda. Since then, WNV has been isolated from mosquitoes, humans, birds, and other vertebrates in Africa, Eastern Europe, western Asia, and the Middle East ([Murgue et al., 2002](#)). From 1975 to 2015 there were several significant outbreaks of West Nile fever. Studies conducted in Egypt in the 1950s showed that the natural history of this disease can dramatically vary. At one extreme are areas where WNV circulates routinely with uncomplicated West Nile fever manifesting as a mild and common childhood disease, which is easily confused with other febrile conditions. In this situation, the heightened infection rate improves background immunity and increases with age. Hence, West Nile fever epidemics and West Nile encephalitis are rare. The other extreme exists in industrialized urban areas, where little or no previous WNV activity has occurred. Here, aging and immunologically naïve populations are likely to encounter WNV for the first time. This leads to West Nile fever epidemics with numerous cases of West Nile encephalitis ([Knudsen et al., 2003](#)).

There have been many West Nile outbreaks throughout the world. Similar to Egypt, Israel experienced outbreaks in the 1950s. In 1957 nursing homes in Israel reported severe neurologic disease and death associated with West Nile fever. An outbreak in Romania is believed to be the catalyst for several outbreaks in large industrialized urban areas.

WNV was first discovered in the United States in 1999. Sixty-two cases and seven deaths (11% case-fatality rate) resulted from it in New York City and the surrounding area. Horses, crows, and exotic birds from a zoo were also found to be infected. Initially, Saint Louis encephalitis virus was believed to be the cause of the human infections until WNV was isolated from the human and animal specimens. This discovery marked the first appearance of WNV in the Western Hemisphere (Jia et al., 1999).

Naturally, there has been some speculation as to how WNV was introduced into the United States. No one really knows for sure. However, the isolates characterized from the 1999 outbreak were shown to be antigenically similar to a strain that circulated in Israel from 1997 to 2000 (Ebel et al., 2001). In 2002 officials at the CDC affirmed that they provided scientists in Iraq with WNV isolates in the 1980s and 1990s. This has led some to believe that the introduction was intentional. The more plausible explanation for a mosquito-borne disease such as this is that the introduction was accidental. Perhaps infected mosquitoes or a reservoir host gained access to the United States via international transportation or trade.

Since the first detected case in 1999 the number of cases and deaths in humans increased dramatically almost every year until reaching a peak in 2006. Table 5.3 presents a summary of West Nile cases in the United States reported between 1999 and 2014.

Horses are affected by WNV infections more often than any other domestic animals. In 2003 there were 4554 horses diagnosed with clinically apparent WNV infection. Ravens, jays, and crows (corvids; family *Corvidae*) serve as a reservoir for WNV. Certain female mosquito species that feed primarily on birds (ornithophilic) enable maintenance of WNV in avian hosts. Other female mosquito species that are not so particular in their blood feeding take up the virus from infected birds and pass them along to other animals. Reservoir competency and field studies suggest that horses or other mammals do not serve as reservoirs for infection, which makes them incidental hosts (McLean et al., 2001).

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### Critical Thinking

West Nile fever burned like a slow-moving wildfire across the United States from New York City to the California coastline in approximately 4 years. Clinicians, public health officials, mosquito control specialists, and animal health professionals all had to come together to mitigate the impact of this emerging disease in the United States. Although much has been done, this serious disease appears to have a foothold on US soil, and cases increased dramatically from 2006 to 2007. When the outbreak was first realized in 1999, some government officials were left to wonder how the pathogen made entry into the United States. Could it have been due to an intentional act?

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**Table 5.3** Number of confirmed human cases and fatalities from West Nile fever reported to Centers for Disease Control by year and clinical presentation in the United States (1999–2014)

Year	Neuroinvasive disease		Non-neuroinvasive disease		Total	
	Cases No.	Deaths No. (%)	Cases No.	Deaths No. (%)	Cases No.	Deaths No. (%)
1999	59	7 (12)	3	0 (0)	62	7 (11)
2000	19	2 (11)	2	0 (0)	21	2 (10)
2001	64	10 (16)	2	0 (0)	66	10 (15)
2002	2946	276 (9)	1210	8 (1)	4156	284 (7)
2003	2866	232 (8)	6996	32 (<1)	9862	264 (3)
2004	1148	94 (8)	1391	6 (<1)	2539	100 (4)
2005	1309	104 (8)	1691	15 (1)	3000	119 (4)
2006	1495	162 (11)	2774	15 (1)	4269	177 (4)
2007	1227	117 (10)	2403	7 (<1)	3630	124 (3)
2008	689	41 (6)	667	3 (<1)	1356	44 (3)
2009	386	32 (8)	334	0 (0)	720	32 (4)
2010	629	54 (9)	392	3 (1)	1021	57 (6)
2011	486	42 (9)	226	1 (<1)	712	43 (6)
2012	2873	270 (9)	2801	16 (1)	5674	286 (5)
2013	1267	111 (9)	1202	8 (<1)	2469	119 (5)
2014	1347	87 (6)	858	10 (1)	2205	97 (4)
<b>Total</b>	<b>18,810</b>	<b>1641 (9)</b>	<b>22,952</b>	<b>124 (&lt;1)</b>	<b>41,762</b>	<b>1765 (4)</b>

Data from ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention.

## Transmission

Worldwide, many different species of mosquitoes have been found to transmit WNV. WNV has been isolated from ticks in Eurasia, but their role in natural transmission of the virus remains elusive. In North America, WNV has been detected in more than 40 different species of mosquitoes. Mosquitoes in the genus *Culex* are the most important vectors for maintaining WNV in nature, but no one knows which species are most responsible for transmission to humans.

As to how WNV persists in the environment is not exactly known. However, studies have shown that several possible mechanisms may work together to provide the opportunities necessary for the virus to survive and thrive. Environmental surveillance studies conducted in New York City after 1999 showed that *Culex* mosquitoes were capable of overwintering in the New York City sewer system. Laboratory studies have shown that transovarial transmission of WNV is possible with *Culex vishnui* mosquitoes. Studies done with birds indicate that contact transmission between birds may occur and that migratory birds may play a role in transporting WNV and its vectors to unaffected regions (Centers for Disease Control and Prevention, 2000).



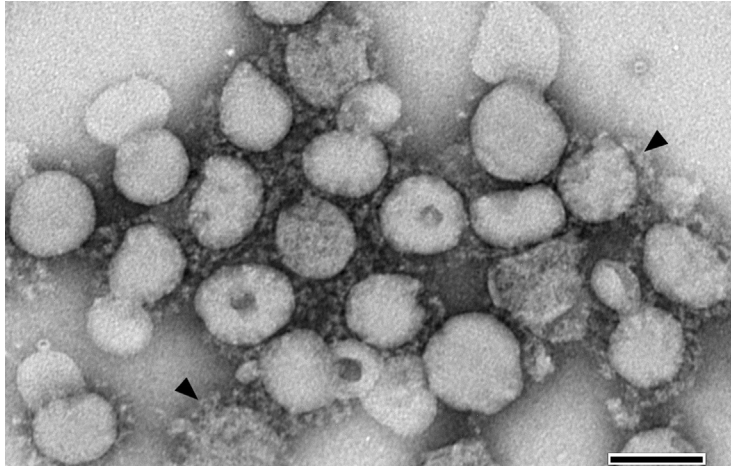
Laboratory-acquired infections have occurred with WNV. In 2002 the CDC documented West Nile fever in two laboratory workers. The first became infected through a wound sustained from a scalpel while removing the brain from an infected blue jay. The second case was from a needle stick to a worker harvesting WNV-infected mouse brains. In 2002 WNV was found to be present in the blood supply. Twenty-three cases of WNV infection were due to infected blood components from 16 WNV-viremic blood donors. This finding prompted blood collection agencies to begin screening blood donations. The following year, 737 donor samples were found to be WNV positive, prompting blood bank officials to discard their donations. Despite the screening, two cases of confirmed blood transfusion-associated West Nile fever were documented in 2003. Nationwide blood screening for WNV has been successful in preventing transfusion-transmitted WNV (Stramer et al., 2005). However, as with all blood donation screening, infections can be transmitted to transfusion recipients on rare occasions despite negative donor test results. Although WNV transmission by blood transfusion is rare, the few cases seen since 2002 underscore the importance of clinical recognition, effective WNV blood screening strategies, and investigation coordination (Pealer et al., 2003).

In August 2002 four patients receiving organ transplants from one organ donor were diagnosed with WNV infection. One of the transplant recipients subsequently died from the infection. The organ donor had received blood products from 63 blood donors to help combat injuries sustained in an accident. Ironically, the last blood transfusion received had been from a WNV-viremic blood donor. Although believed to be rare, transplacental transmission of WNV is possible, with one confirmed case taking place in 2002.

### **Clinical Presentation, Diagnosis, and Treatment**

The incubation period for WNV is approximately 3–14 days. Epidemiologists believe that approximately 80% of people infected with WNV are asymptomatic. Approximately 20% of those infected develop a mild illness, termed West Nile fever. Uncomplicated West Nile fever typically begins with sudden onset of fever, headache, lymphadenopathy, and myalgia, often accompanied by gastrointestinal symptoms. The acute illness usually lasts 3–6 days, but prolonged fatigue is common. In earlier epidemics in which West Nile fever cases predominated, nearly half of all case patients presented with a maculopapular rash.

Less than 1% of WNV infections result in severe neurological disease. The more severe form of the disease is referred to as West Nile encephalitis, West Nile meningitis, or West Nile meningoencephalitis. *Encephalitis* refers to an inflammation of the brain, *meningitis* to an inflammation of the membrane around the brain and the spinal cord, and *meningoencephalitis* to inflammation of the brain and the membrane surrounding it. The symptoms of these severe infections include headache, high fever, neck stiffness, stupor,



**Figure 5.4** This is a negatively stained transmission electron micrograph from a tissue culture isolate, revealing numbers of severe acute respiratory virus virions, which are members of the family Coronaviridae. Courtesy of US Health and Human Services, Public Health Image Library.

disorientation, coma, tremors, convulsions, muscle weakness, and paralysis. Severe neurological disease due to WNV infection may occur in patients of all age groups. Year-round transmission is possible in some areas.

## SEVERE ACUTE RESPIRATORY SYNDROME VIRUS

SARS appeared as an outbreak in China very suddenly in 2003. SARS serves as an example of a Category C disease because of the many challenges government agencies faced from a newly emerging disease, which seemingly came out of nowhere. What caused it was never seen before coronavirus (Fig. 5.4). The coronavirus that causes SARS is highly infectious. Some of the patients from this outbreak were referred to as *super-spreaders* because they shed so much virus they infected many other people. The initial outbreak that had the world's attention occurred in May 2003 in Hong Kong, but an epidemiological investigation showed the true origin led back to China's Guangdong province.

Guangdong is one of the more prosperous areas of China. It can be characterized as an area dotted with industrial complexes surrounded by fertile farmlands, where people work and live in close proximity to their animals. Animals are an important part of life in Guangdong. In fact, much of South China is known for its live animal markets. In this region, the Chinese believe that eating freshly killed wild animals promotes vitality and good health. In the live animal markets, you may purchase cats, dogs, snakes, bats, and civets. Once you make your purchase the animal is butchered for the customer to take home.

SARS is believed to have developed here in the live markets or farm settings of Guangdong province. On November 16, 2002, a 45-year-old man in Foshan, a Guangdong city of 3.4 million, became ill with an unusual respiratory illness (Knobler et al., 2004). No one knows exactly where or how he contracted the illness. He had no travel history, but he had recently prepared chicken, cat, and snake for household meals. An epidemiological investigation showed that many of the earliest SARS case patients had possible associations with the use of wild animal food sources. The man, a local leader in the province, was married with four children. Within weeks, his wife, a niece, an aunt, and her husband also became ill (Xu et al., 2004). The initial case patient and his four family members are thought to have been the first cluster of a disease that infected 8096 people around the world and killed 774 before ebbing in the summer of 2003 (9.5% case-fatality rate). Guangdong was especially hard-hit, accounting for more than 1500 probable cases and 58 deaths.

It took months after this first known infection for health authorities throughout the world to identify the disease as something new, learn its characteristics, and determine how to deal with it (Goldsmith et al., 2004). In the early days of SARS, little was known by anyone anywhere about this mysterious disease. Medical workers had no diagnostic criteria and no clinical test, and the incubation period was unknown. The method of transmission was uncertain, as was the effectiveness of protective equipment and safety requirements. SARS spread from Foshan into other areas of Guangdong. By January 2003 it was seen in Guangzhou, the provincial capital, where workers in the health industry began to fall ill.

SARS was a tragedy. In the space of a few months the deadly virus emerged from the jungles of central China and moved to several other countries by various means of transportation. In Canada SARS caused severe illness in more than 3300 people. Southern Ontario was the worst-affected jurisdiction outside of Asia, with SARS infecting 375 people and killing 44 (SARS Commission, 2006).

It caused untold suffering to its victims and their families, forced thousands into quarantine, brought the health system in the greater Toronto area and other parts of the province to its knees, and seriously affected health systems in other parts of the country. In addition, travel advisories issued by the World Health Organization and the CDC, advising people to avoid all travel to Ontario, caused the local economy there to suffer great losses. Nurses lived daily with the fear that they would die or infect their families with a fatal disease. Respiratory technicians, doctors, hospital workers, paramedics, and home care workers lived with the same fear. Of the almost 375 people who contracted SARS in Ontario, 72% were infected in a health-care setting. Of this group, 45% were health workers (McDonald et al., 2004). Most of these workers were nurses whose jobs brought them into the closest contact with sick patients. This does not show the full burden of SARS on nurses, paramedics, and other health workers. In many cases nurses sick with undetected SARS brought illness, and in some cases death, home to their families (SARS Commission, 2006).

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## SARS and Public Health

As mysteriously as it appeared the deadly SARS virus was contained and put to rest. Hundreds of cases were dealt with in several countries connected by international travel routes to China. Case-fatality rates were very high. Infection control procedures, isolation, and quarantine all were needed to contain the problem. However, the global public health community managed to muster an amazing effort, which now speaks volumes about the importance of public health education, surveillance, and modern technology. Is this indicative of how all new emerging disease threats will be handled?

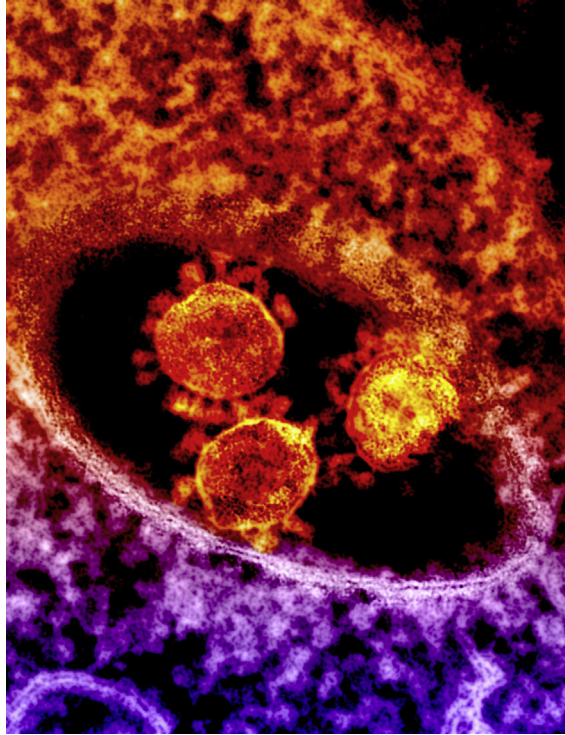
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## Lessons Learned With SARS

- Despite the unwillingness of the Chinese government to share information from the initial cases in this outbreak, the world health community collaborated in an unprecedented manner. A consortium of laboratories managed to sequence the genome of this newly discovered pathogen in a few days to develop rapid diagnostic and surveillance tools.
- International travel played a tremendous role in the spread of SARS. This shows us that the connectedness of our cities and populations can spread a deadly pathogen from one side of the world to the other in hours.
- Health-care facilities played an important role in the epidemiology of SARS. Patients infected with the SARS-coronavirus disease are likely to present to health-care facilities. If unrecognized as SARS, then these patients may transmit SARS to health-care workers and other patients. Health-care workers accounted for a significant percentage of cases in most major SARS outbreaks reported.
- Is coronavirus just a relic? A coincidence? Some people with the disease were not presenting with antibodies to coronavirus, whereas there were some people showing no signs of the disease that were positive for antibodies to coronavirus. This finding is still very puzzling to many. Because the outbreak was so short-lived we do not know how this disease might affect a large population or what role asymptomatic or subclinical patients play in the dynamics of disease transmission.
- AIDS patients did not seem to be affected by the SARS coronavirus. That fact is very puzzling to researchers.

## MIDDLE EAST RESPIRATORY SYNDROME

MERS is a respiratory illness caused by a coronavirus called Middle East respiratory syndrome coronavirus (MERS-CoV). Refer to [Fig. 5.5](#) for a colorized electron micrograph of MERS-CoV. Similar to SARS, MERS patients develop severe respiratory illness. Nearly 40% of MERS cases are fatal ([Jalal, 2015](#)).



**Figure 5.5** This highly magnified, digitally colorized transmission electron micrograph reveals ultrastructural details exhibited by several red-colored, spherical-shaped Middle East respiratory syndrome coronavirus virions. Note the similar structural appearance to the severe acute respiratory system virus. *Courtesy of US Health and Human Services, Public Health Image Library.*

This emerging disease was first reported from an outbreak of serious respiratory case patients in Saudi Arabia in September 2012 (Hui, 2013). However, through retrospective investigations, health officials later identified that the first known cases of MERS occurred in Jordan in April 2012. Since the initial outbreak, MERS-CoV has spread to many other countries in the Arabian Peninsula and to Europe, the United States, and South Korea.

### Transmission

The primary means of transmission of MERS-CoV is from person to person, primarily through coughing. MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. Infected people have spread MERS-CoV to others in health-care settings, such as hospitals. Researchers studying MERS have not seen any ongoing spreading of MERS-CoV in the community (Cotton et al., 2013). Most infected people either lived in the Arabian Peninsula or recently traveled from the Arabian Peninsula before they became ill. A few people became infected with MERS-CoV after having close contact with an infected person who had recently

traveled from the Arabian Peninsula. So far all cases of MERS have been linked to countries in and near the Arabian Peninsula.

### **Clinical Presentation, Diagnosis, and Treatment**

Most people confirmed to have MERS-CoV infection have had severe acute respiratory illness with the symptoms of cough, high fever, and shortness of breath. Some MERS patients also have gastrointestinal symptoms of diarrhea, nausea, and vomiting. The most serious cases come from the development of severe complications, such as kidney failure and pneumonia. In fact, most of the people who died had an underlying medical condition. Patients with mild symptoms recover well (Hui, 2013).

It is currently believed that people with preexisting medical conditions (eg, diabetes) are more likely to become infected with MERS-CoV or have a severe case. Individuals with weakened immune systems are also at higher risk for getting MERS or having a severe case. The incubation period for MERS is thought to be 5 or 6 days, but it can range from 2 to 14 days (Zumla et al., 2015).

There is no US Food and Drug Administration approved test for MERS. Instead, experimental assays are run in CDC or WHO reference laboratories. Molecular tests, such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays, are used to diagnose active infection in MERS case patients. The WHO's current case definition for laboratory confirmation of MERS-CoV infection requires either a positive rRT-PCR result for at least two specific genomic targets or a single positive target with sequencing of a second target. Serological testing is used to detect previous infection (antibodies to MERS-CoV) in people who may have been exposed to the virus. The presence of antibodies to MERS-CoV indicates that a person had been previously infected with the virus and developed an immune response.

There is no specific antiviral treatment recommended for MERS. Patients need to be identified rapidly and put into medical isolation. Current treatment for severe cases is supportive care with emphasis on support of vital organ (liver, kidneys, lungs, etc.) functions.

### **CONCLUSION**

Emerging diseases present a very unique challenge to public health officials and infectious disease specialists. Perhaps they have been with us for millions of years, lurking in a dark corner of the environment, waiting for an opportunity to jump from their natural cycle of transmission to a human host. Or they may represent something totally new. Regardless of their origin, an emerging disease pathogen must be characterized quickly by molecular biologists and microbiologists. The dynamics of disease transmission must be investigated by teams of epidemiologists. Treatment regimens must be formulated by clinicians working on the front lines of the outbreak. Disease prevention strategies and risk communications must be quickly formulated by public health officials. Finally,



media attention for emerging disease outbreaks forces government officials at all levels to address the problem with planning and preparedness activities aimed at preserving the health of the public. Category C agents may be exploited in much the same way that hoax powder incidents followed the 2001 Amerithrax event. In addition, terrorist groups and rogue states might take advantage of the emergence of one of these special pathogens to intentionally introduce an emerging disease into an area, thereby causing fear, panic, and social disruption.

## ESSENTIAL TERMINOLOGY

- **Emerging disease.** Any disease, of various causes, that has newly appeared or is rapidly expanding its range in the human species.
- **Hantavirus.** One of the four genera of the family Bunyviridae. Hantaviruses are spread by rodents and target the kidneys, lungs or pulmonary system, and heart. The word *hantavirus* is derived from the Hantaan River, where the Hantaan virus (the etiologic agent of Korean hemorrhagic fever) was first isolated. The disease associated with Hantaan virus is called Korean hemorrhagic fever or hemorrhagic fever with renal syndrome.
- **Nipah virus fever.** A febrile illness caused by Nipah virus, a virus in the genus *Henipavirus* of the family *Paramyxoviridae*. Henipaviruses are characterized by their large size, natural occurrence in *Pteropid* fruit bats, and recent emergence as zoonotic pathogens capable of causing illness and death in domestic animals and humans.
- **Middle East respiratory syndrome (MERS).** Caused by MERS–coronavirus, MERS first appeared in Saudi Arabia in 2012, but it is thought to have originated from Jordan that same year. Similar to SARS, it causes severe respiratory disease and pneumonia with a high mortality rate. All outbreaks of this emerging disease can be traced back to the Arabian Peninsula.
- **Severe Acute respiratory syndrome (SARS).** SARS is an atypical form of pneumonia. It first appeared in November 2002 in Guangdong Province, China. SARS is caused by the SARS coronavirus, a novel coronavirus.
- **West Nile fever.** A febrile illness caused by West Nile virus, which is transmitted from birds to people through the bite of an infected *Culex* mosquito. The virus is closely related to other flaviviruses including those responsible for St. Louis encephalitis, Japanese encephalitis, and Murray Valley encephalitis.

## WEBSITES

Food and Agriculture Organization (FAO), Manual for Diagnosis of Nipah Virus Infection in Animals. <http://www.fao.org/docrep/005/ac449e/ac449e00.htm>  
 World Health Organization, Nipah Virus Overview. <http://www.who.int/csr/disease/nipah/en/>

Centers for Disease Control and Prevention. Facts About Hantavirus. [http://www.cdc.gov/hantavirus/pdf/hps\\_brochure.pdf](http://www.cdc.gov/hantavirus/pdf/hps_brochure.pdf)

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