Introduction

The henipaviruses are a recently described genus of zoonotic viruses, two of which have been recognized to cause outbreaks in humans as well as animals. Although relatively rare, Nipah virus (NiV) and Hendra virus (HeV) both have the potential for significant economic impact due to epidemics in animal populations, as well as human disease with potential for person-to-person, including nosocomial, transmission. In humans, both diseases are highly lethal, and medical countermeasures are in very early stages of development. Outbreaks due to these viruses have been identified only in Australia and southern and southeast Asia; however, the animal reservoir, bats of the Pteropodidae family, have a wide distribution that includes Africa, and evidence for henipaviruses in bats has been documented as far as West Africa. A wide range of mammalian species can be infected experimentally with the henipaviruses and multiple animal models exist for research, but no wild reservoirs other than bats have been identified. Both Hendra and Nipah viruses are considered biosafety level 4 pathogens.

Nipah virus (NiV)

Nipah virus was first recognized as a cause of human disease after an outbreak in Malaysia in 1998–99. The outbreak of encephalitis was orig-
inally thought to be due to Japanese encephalitis, but in March 1999 a novel paramyxovirus was identified from the cerebrospinal fluid of an individual from Sungai Nipah village. This outbreak was associated with pigs and pig farming, and was transported to Singapore via infected carcasses. It is proposed that pigs raised in large-scale pig farms became infected by ingestion of fruit contaminated with bat saliva, as the reservoir fruit bats are found in proximity to the farms and frequently drop partially consumed fruit. There was very little evidence of person-to-person spread in the Malaysia/Singapore outbreak. The vast majority of cases were associated with direct contact with the pigs. Later outbreaks in Bangladesh and India, in contrast, have been associated primarily with consumption of date palm sap contaminated with bat excreta, and human-to-human transmission, including in health care facilities, has been a prominent concern. Other animals have also been found to be infected, including cows, goats, cats, and dogs. A significant outbreak in the Philippines occurred in 2014 in horses. Some transmission may have been associated with these domestic animals, including by ingestion of infected horsemeat. The virus is highly contagious among pigs, which produce copious secretions, with high morbidity rates but relatively low mortality.

Humans develop disease ranging from asymptomatic infection to severe encephalitis and death, although asymptomatic disease appears to be rare. A respiratory component is common, affecting approximately half of patients with severe neurologic signs, and exposure to respiratory secretions is the most likely means of person-to-person transmission. There may be some strain differences; for example, in the Malaysia outbreak, severe respiratory symptoms were much less common than in the subsequent Bangladesh and India outbreaks. The incubation period is described as 4–14 days, with initial fever, headache, vomiting, and sore throat, with or without respiratory symptoms such as cough or respiratory distress. In Bangladesh, significant frothing at the nose and mouth was described in late stages. In severe cases there is eventual development of lethargy and confusion with potentially rapid development of seizures and coma. If fatal, death occurs most commonly within 1–2 weeks. Case fatality rates have ranged from 40% to 75%. Higher rates were frequently found in settings where intensive care was not available.
or accessed. Among survivors of encephalitis, approximately 20% to 30% will suffer some neurologic sequelae. Additionally, there have been reports of relapse or late-onset encephalitis.

The diagnosis of NiV infection is made by immunohistochemistry, RT-PCR or conventional PCR of respiratory secretions, tissues, or cerebrospinal fluid, or serology by ELISA.

There are no approved vaccines or therapeutics for either of the henipaviruses. Vaccine trials in both livestock and humans are under way, as are trials of antivirals and antibody-based therapies.

Transmission, Infectivity, and Contagion. Most cases of Nipah virus disease in humans have been due to transmission from zoonotic hosts, either by contact with respiratory secretions (such as those from pigs) or other bodily fluids, or through ingestion of excreta (of bats in palm sap) or tissues of infected animals (pigs, horses). Infection of humans may also occur by ingestion of fruit contaminated by bats, but that association has not been demonstrated clearly.

Person-to-person transmission is clearly associated with close contact. Highest risk is associated with contact with persons who died (presumably with higher viral loads) and via contact with respiratory secretions and saliva. Handwashing and avoidance of the ill person have been associated with protection. The virus has also been isolated from urine, and has been recovered from sheets and towels. Epidemiologic investigation suggests that close exposure to saliva and respiratory secretions of an ill person presents a very high risk, and towels used by caregivers for more than one patient may act as fomites. During the Malaysia/Singapore outbreak, person-to-person spread was rare. This may have been due to both a lower rate of respiratory symptoms in patients and to relatively stronger infection control practices in homes and care facilities. Health care workers who reported blood and body fluid exposures to skin and mucous membranes, and even needlesticks, did not become infected. In Bangladesh, transmission to household care providers and nosocomial transmission to informal care providers and other patients was common, but transmission to health care workers was not. Epidemiologic and anthropologic studies suggest that within health care facilities most nursing care was given by friends and family rather than formal health care providers. Such care in homes and facilities
provided multiple opportunities for exposure to respiratory secretions including cleaning; kissing, whispering to, and spoon-feeding the patient; and finishing food partially consumed by the ill patient, particularly at the end of life. Health care workers in Bangladesh who reported exposures did not have evidence of seroconversion. However, in some outbreaks in India, where more intensive care was provided (including nasogastric tubes and intubation) but infection control practices were poor, the risk to health care workers in facilities was higher. In at least one case, transmission was linked to the performance of funeral rites, which included cleaning of the orifices of the corpse, including the mouth and nasal cavities, without personal protective equipment (PPE). It is reasonable to assume that such activity would confer risk, but a pattern of funeral-related outbreaks has not been clearly observed. However, individuals involved in funeral rites are often the same persons who have been caregivers, so separating those risk factors is difficult.

It has also been recognized that some individuals appear to be “super-spreaders” and are responsible for a high proportion of secondary cases. Characteristics that define a super-spreader appear to be more related to host factors than to viral traits and may include viral load, underlying immune status, ability to produce secretions, and social status (high social status results in more contacts).

*Need for Quarantine of Exposed Persons.* Thus far, no serosurveys of persons without disease but with a history of exposure to known cases, have indicated a significant risk of asymptomatic infection. In addition, the risk of transmission is highest from patients who died, suggesting that severity of disease correlates with contagiousness. Respiratory secretions of patients with pulmonary symptoms appear to be the most common means of transmission. Hence, quarantine of asymptomatic exposed persons seems unlikely to provide benefit. Close surveillance of caregivers and close household contacts for the development of symptoms is reasonable, however, and has been implemented in previous outbreaks.

*Isolation of Symptomatic Persons.* Although the data is incomplete, available information suggests that direct contact with respiratory secretions and droplets from symptomatic patients are the major risk for person-to-person and nosocomial transmission. Significant nosocomial
spread to persons with near, but not direct, contact in enclosed hospital settings, including to other patients and their caregivers, has been documented, although this typically occurs in the setting of recognized pulmonary symptoms and coughing without the use of personal protective measures. The epidemiology does not suggest airborne spread in general, but other paramyxoviruses such as measles can be transmitted in that manner, so that possibility exists, especially in the setting of aerosol-generating procedures.

Current recommendations from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) emphasize contact and droplet precautions. Most nosocomial transmission has occurred in settings with poor infection control practices, so determination of whether more aggressive measures are warranted is difficult. WHO-supported Bangladeshi guidelines recommend isolation in a separate ward and barrier precautions including mask, gown, gloves, and shoe covers, with enforced hand hygiene. An N-95 mask is recommended for procedures with an aerosol risk such as intubation and suction. Eye protection is not mentioned. It should be noted that these guidelines are recommended in the setting of very minimal baseline infection control practices in many facilities of the country and would be difficult to achieve in some settings. In a more resourced setting, it would be reasonable to recommend eye protection be added for the care of a patient with any pulmonary symptoms.

*Need for High-Level Isolation.* Consideration of whether a patient should be treated in a specialized isolation unit is based on a combination of factors, including the infectivity of the pathogen (including infectious dose), case fatality rate, modes of transmission, availability of resources, and availability of medical countermeasures. Historical epidemiologic information can inform risk assessment but may not be applicable to highly resourced settings. In the case of Nipah virus, most nosocomial transmission has occurred in settings where even basic standard precautions were not available, and initiation of contact and droplet precautions would be expected to reduce transmission. However, options for medical countermeasures are limited, and this fact, combined with the high case fatality of NiV infection, might prompt the consideration of more stringent isolation conditions in highly resourced
settings. Furthermore, in more highly resourced settings the likelihood of interventions that might aerosolize respiratory secretions is higher. The European Network of Infectious Diseases recommended airborne precautions at a minimum for “Hendra-like” viruses with the optimal situation involving high-level containment. An informal survey of clinicians working in high-level containment care (HLCC) units indicated that 44% would treat “Hendra-like” viruses in an HLCC unit; the balance favored either standard hospital setting or a case-by-case decision. Factors that would favor treatment in an HLCC unit would include copious respiratory secretions and potentially gastrointestinal secretions; there is little data to support shedding of virus in stool in humans, but it has been isolated from human urine and gastrointestinal fluids from bats. The need for invasive procedures such as intubation would also factor in the decision, as would severity of illness.

Termination of Isolation Precautions. There is very little data to guide the discontinuation of isolation precautions. However, data from one study suggests that viral shedding declines with the development of immunoglobulin M (IgM) antibodies, so it is probably reasonable to discontinue isolation as clinical condition improves and respiratory symptoms resolve.

Hendra virus (HeV)

Hendra virus (HeV), originally known as equine morbillivirus, was first identified in an outbreak in horses in 1994 in Queensland, Australia. Since then several other outbreaks have occurred in Australia, affecting more than 70 horses as of 2016. Only 7 cases in humans have been reported, 4 of which were fatal. All were in persons who had very close contact with sick horses, such as performing autopsies without appropriate PPE or very heavy exposure to secretions. There have been no human-to-human transmissions, and multiple other persons who had contact with ill horses did not develop disease. Illness in both humans and horses can include a severe respiratory syndrome that can progress to encephalitis. As with Nipah virus, fatal recrudescence neurologic disease has occurred.

Also, as with Nipah virus, diagnosis is typically made by RT-PCR, se-
rology, viral isolation, or immunohistochemistry of tissues. No specific vaccine for humans exists; antiviral and antibody-based therapies are in early trials.

**Considerations for Quarantine, Isolation, and Infection Control.** Quarantine is not recommended for contacts of human or animal cases, and Australian infection control policy does not recommend restriction of movement for asymptomatic contacts. Given the lack of evidence for human-to-human transmission, and epidemiologic evidence suggesting that a heavy exposure is needed to result in human infection, there are few guidelines suggesting the need for high-level isolation. South Australian health guidelines recommend that persons infected with Hendra virus be restricted from work, childcare, day care, and school until well. Australian infection control guidelines recommend standard, contact, and droplet precautions for most care, with airborne precautions if aerosol-generating procedures are likely. Considerations for high-level isolation would be similar to those for NiV, with the caveat that human-to-human transmission appears to be less common than with NiV, and also acknowledging the limited number of human data from which to make recommendations.

**Severe Fever with Thrombocytopenia Syndrome**

Severe fever with thrombocytopenia syndrome virus (SFTSV) is a recently described Phlebovirus belonging to the *Bunyaviridae* family. It is transmitted by ticks, primarily *Haemaphysalis longicornis* but also *Rhipicephalus microplus*. The former feeds on domestic animals, and serosurveys of these animals have revealed seroprevalence rates of up to 75% in chickens, goats, cattle, and sheep. Wild animals have lower rates of seroprevalence. These zoonotic hosts may have no or mild symptoms but may act as amplifying hosts. A specific primary zoonotic reservoir has not been identified.

Disease in humans was first identified in China in 2007, and several outbreaks have occurred there as well as South Korea and Japan. Case fatality rates have been as high as 30%. Most cases occur in adult farmers, but human-to-human transmission has occurred, including in nosocomial settings. The incubation period, at least from person-to-person
cases, has been described as 8–13 days. Clinical presentation of disease begins with fever, followed by development of leukopenia and thrombocytopenia and biochemical evidence of organ dysfunction. Diarrhea (including melena) and vomiting (including hematemesis) have been reported as significant; respiratory symptoms have been less prominent, although respiratory failure can occur as a component of multi-organ system failure.

Reviews of risk factors for human-to-human transmission suggest that direct exposure to blood or respiratory secretions is the most common route. Whether respiratory secretions uncontaminated by blood are infectious is unclear as most of the source patients had bloody secretions or coincident hematemesis. Contacts of patients who did not participate in close care of the ill person or in funeral preparations were less likely to develop disease. Investigation of one cluster suggested that contact with nonbloody secretions resulted in asymptomatic infection, whereas contact with bloody secretions was associated with symptomatic disease. In general, infected health care providers were not using full barrier precautions.

Considerations for Quarantine, Isolation, and Infection Control. At the current time there is no evidence for transmission from asymptomatic persons, whether with incubating disease or with asymptomatic infection. Quarantine measures have not been recommended for exposed persons. Isolation for persons with clinical disease should clearly include contact precautions, and droplet precautions including eye protection would be recommended for many ill patients, especially if producing copious bodily secretions. Airborne precautions would be appropriate for procedures expected to generate aerosols. Considerations for care in high-level containment would be similar to those for other hemorrhagic fevers, although the data so far suggest that transmission does not occur as easily as with the filoviruses. Factors in favor of a higher isolation level would include hemorrhagic manifestations, especially complicating gastrointestinal losses, and the need for high-intensity interventions.

Plague

Plague, caused by the bacterium *Yersinia pestis*, is not a new disease, and in the most common form (bubonic) is not considered a significant risk
for nosocomial spread. However, nosocomial transmission has occurred with the pneumonic form. The last such reported case in the United States was in the early 20th century, but more recent episodes have been documented in less resourced areas.

Infection with *Y. pestis* most commonly occurs from the bite of an infected flea, but the blood and tissues of a patient can be infectious. Transmission from an individual with pneumonic plague typically follows a droplet pattern, although as with other pathogens, certain procedures may carry a risk of aerosolization, including manipulation of the respiratory tract and some autopsy procedures.

Existing guidelines for the management of plague recommend contact precautions, and droplet precautions until either the pneumonic form has been excluded or treatment has been ongoing for 72 hours. Airborne precautions are warranted for certain procedures. High-level isolation has not been employed typically for the care of patients with plague. Most nosocomial transmission has occurred before the diagnosis was determined and in the absence of personal protective measures. Options for therapy and postexposure prophylaxis exist (antibiotics), and vaccines are available, although not currently produced in the United States.

**Extensively Drug-Resistant Tuberculosis**

Infection with tuberculosis (TB) is well known to be a risk for health care workers and other individuals in health care facilities, especially in environments where rigid infection control measures are not in place. Presumably the risk is similar for extensively drug-resistant TB (XDR-TB), and increased incidence of multidrug-resistant TB (MDR-TB) and XDR-TB has been documented in health care workers in areas with a high prevalence. However, transmission of TB, including XDR-TB, is almost universally via the airborne route, with small suspended airborne particles inhaled into alveoli; droplet and direct contact, including to mucous membranes, are negligible risks. There is no evidence of failure of appropriate airborne precautions to prevent transmission of XDR-TB to health care workers once a case is diagnosed. In addition, medical countermeasures (antituberculous antimicrobials) do exist for treatment and postexposure prophylaxis, although the regimens are relatively
complicated and of long duration. High-level isolation precautions have not typically been recommended. However, increased environmental controls such as appropriate ventilation, negative pressure, and use of germicidal ultraviolet light; availability of respirators; and rapid diagnosis and initiation of therapy are important to reduce nosocomial transmission to health care workers and other patients. Forcible quarantine has been utilized in public health practice in situations where individuals fail to adhere to their antituberculous regimens and therefore pose a public health risk to others. Decisions on how and when to do this generally occur at the local level, although there is now a federal quarantine center at the University of Nebraska Medical Center. How that might be used related to cases of tuberculosis remains to be determined.

**Rabies**

Rabies, caused by the rabies virus, is a disease resulting almost uniformly in death and with few reliable medical countermeasures available once symptoms have developed. However, rabies has not been documented to have been transmitted nosocomially, and, outside of organ transplantation, there is only one anecdotal report of possible human-to-human transmission in the literature. Transmission typically occurs via transdermal or mucous membrane exposure to saliva of infected animals. Similar exposure to neurologic tissue can theoretically result in infection as well. Acquisition by inhalation of aerosols of bat excreta has been proposed but never confirmed. There are effective pre- and postexposure vaccination strategies for health care workers who come in contact with potentially infectious material (primarily saliva); postexposure prophylaxis is not recommended for casual contact, including that involving blood, urine, or feces of an infected person or animal. Current experience does not support the need for care in an HLCC unit.