

Nipah Virus Infection

*Nipah Virus Encephalitis,
Porcine Respiratory and
Encephalitis Syndrome,
Porcine Respiratory and
Neurologic Syndrome,
Barking Pig Syndrome*

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Importance

Nipah virus infection is an emerging disease endemic in Southeast Asia. This virus is carried subclinically in fruit bats of the genus *Pteropus*, a host to which it seems well adapted. Illnesses caused by Nipah virus were first described in 1998-1999, during widespread outbreaks among pigs and people in Malaysia. The virus had apparently been transmitted from bats to pigs around 1996, and was thereafter maintained in swine populations. It was not detected immediately, as the mortality rate was low and the illness resembled other pig diseases. Nipah virus subsequently spread to pig farmers and abattoir workers in Malaysia and Singapore, causing severe, often fatal, encephalitis in more than 250 people. Some other species, including cats, dogs and goats, were also affected. The Malaysian outbreaks were controlled in both domesticated animals and humans by culling more than one million pigs. In addition, pig farming was permanently banned in some high-risk areas.

While Nipah virus encephalitis has not been documented in Malaysia since that time, human cases have been reported regularly in Bangladesh and a neighboring region of northern India since 2001. Many of these cases seem to be acquired directly from bats by drinking raw date palm sap, a widely consumed local delicacy. The sap is thought to become contaminated when bats visit and drink from unprotected sap collection sites at night. Person-to-person transmission also occurs after close, unprotected contact. How widely Nipah virus circulates in bats is still uncertain; however, viral RNA and seropositive bats have also been identified in areas where no clinical cases have ever been reported. A recent outbreak of neurological disease in horses and humans in the Philippines also appears to have been caused by this virus.

Etiology

Nipah virus is a member of the genus *Henipavirus* in the family Paramyxoviridae. This genus also includes Hendra virus, Cedar virus (an apparently nonpathogenic virus found in Australian bats) and additional uncharacterized henipaviruses in various locations.

There seem to be multiple strains of Nipah virus. At least two major strains were isolated from pigs in Malaysia, and the strains that cause human cases in Bangladesh and India differ from outbreak strains isolated in Malaysia. A henipavirus that recently caused an outbreak in the Philippines is also thought to be Nipah virus, based on RT-PCR results. It appears to be most similar to the viruses from Malaysia.

Species Affected

Fruit bats of the genus *Pteropus* (flying foxes) are the main reservoir hosts for Nipah virus. *P. vampyrus*, the Malayan flying fox, and *P. hypomelanus*, the island flying fox, are known to carry this virus in Malaysia. *P. giganteus* is thought to be an important host in Bangladesh and India and possibly other locations. Although live virus has not yet been isolated from this species, Nipah virus RNA has been detected and many bats are seropositive. Nipah virus also occurs in *P. lylei* in Thailand and Cambodia, and *P. poliocephalus* has been infected experimentally. Viral RNA and/or antibodies have been found in a few other species of fruit or insectivorous bats, although their significance is unclear.

Many domesticated mammals seem to be susceptible to Nipah virus. This virus can be maintained in pig populations, but other domesticated animals appear to be incidental (spillover) hosts. Sick goats, dogs, cats and horses were observed in the outbreak area in Malaysia, and infections in dogs, a cat, a horse and goats were confirmed by immunohistochemistry. Sheep might also have been affected, but there are no confirmatory data, and no evidence of infections could be found in rats. Nipah virus seems to have affected horses in the Philippines in 2014, based on clinical signs in the horses and epidemiological links to human patients; however, no tissues were available from the horses for confirmation. Several cats and a dog that had eaten tissues from sick horses in the Philippines also died, and seropositive dogs were reported in the outbreak area. Another study reported seropositive cattle, pigs and goats in Bangladesh; however, these antibodies did not neutralize Nipah virus, and could have been caused by related henipaviruses.

Experimental infections with Nipah virus have established in pigs, cats, ferrets, nonhuman primates, guinea pigs, golden hamsters (*Mesocricetus auratus*) and mice.

Zoonotic potential

Nipah virus can cause serious illnesses in people. A number of cases have been linked to drinking raw date palm sap, which had probably been contaminated by bats. Drinking fermented date palm sap (alcohol content approximately 4%) appeared to be a risk factor in a few cases. Zoonotic cases were acquired from pigs in Malaysia (bat to human transmission appears to be uncommon or absent in this area), while people who became infected in the Philippines had either eaten undercooked meat from sick horses or participated in their slaughter. A few cases in Bangladesh and Malaysia might have been acquired from sick animals of other species (a dog, various livestock), but the evidence in these cases was speculative and/or circumstantial.

Geographic Distribution

Nipah virus might be endemic across much of Southeast Asia; however, confirmed cases in humans and/or domesticated animals have only been reported in Malaysia, Bangladesh and nearby areas of northern India. The virus that caused an outbreak in the Philippines has not been completely characterized yet, but it also appears to be Nipah virus. Abattoir workers in Singapore became ill after contact with infected pigs imported from Malaysia; however, there is no evidence that this virus is endemic among pigs in Singapore. Nipah virus has been isolated from bats in Cambodia, and viral RNA has been detected in bats in Thailand and East Timor. Antibodies to Nipah virus or other henipaviruses have been found in bats in additional Asian countries (e.g., China, Vietnam) and on other continents; however, viral and serological evidence suggests that at least some of these viruses might be distinct viral species.

Transmission

In *Pteropus* bats, Nipah virus has been found repeatedly in urine, and viral RNA has been detected rarely in oropharyngeal swabs and rectal swabs from naturally or experimentally infected bats. It has also been found in fruit that had been partially eaten by bats. Despite high seroprevalence rates, only a few bats in a colony may shed the virus at any given time, and excretion from the colony may be sporadic.

How bats transmit this virus to domesticated animals is uncertain, but ingestion of contaminated fruit, water, or aborted bat fetuses or birth products (e.g., by pigs) is suspected. Nipah virus is highly contagious in swine, which can act as amplifying hosts and shed this virus in respiratory secretions and saliva. Experimental infections suggest that shedding may start as early as 2 days after infection and persist for up to 3 weeks. During the Malaysian outbreak, Nipah virus appeared to be transmitted within a farm by aerosols and direct contact between pigs; virus spread between farms was usually

associated with pig movements. Although this virus has not been reported, to date, in the urine of pigs, it can occur in the kidneys, and exposure to pig urine is a risk factor for human infections. Anecdotal evidence suggests that vertical transmission may occur across the placenta. Transmission in semen may be possible, and re-used vaccination needles may have contributed to the spread of the virus between pigs in Malaysia.

Cats can be infected experimentally by intranasal and oral inoculation, and they can shed Nipah virus in respiratory secretions and urine. Cats and a dog that died in the Philippines had recently eaten meat from infected horses. *In utero* transmission has been demonstrated in cats, with the detection of virus in the placenta and embryonic fluids. Although experimental studies have not been published in dogs, serological surveys in Malaysia suggest that Nipah virus did not spread horizontally in dogs during this outbreak.

Humans can be infected by direct contact with infected swine, probably through the mucous membranes, but possibly also through skin abrasions. During a recent Nipah-like outbreak in the Philippines, most patients had been involved in slaughtering sick horses or had eaten undercooked horsemeat from sick horses. In Bangladesh, human cases have been linked to drinking unpasteurized date palm sap (juice). Oral transmission, using artificial palm sap spiked with Nipah virus, and respiratory transmission were both demonstrated in a hamster model. Person-to-person transmission can occur after close direct contact, and has been common during some outbreaks in Bangladesh and India. Humans can shed Nipah virus in respiratory secretions, saliva, and urine, and contact with respiratory secretions is thought to be the main route of spread. Some people also became ill after unprotected contact with deceased patients, such as during preparation of the corpse for burial. Nosocomial transmission has been documented in hospitals where infection control measures are inadequate; however, the risk to healthcare workers appeared to be low in Malaysian hospitals.

How long Nipah virus can remain viable in the general environment is uncertain; however, it can survive for up to 3 days in some fruit juices or mango fruit, and for at least 7 days in artificial date palm sap (13% sucrose and 0.21% BSA in water, pH 7.0) held at 22°C. This virus is reported to have a half-life of 18 hours in the urine of fruit bats.

Disinfection

Like other paramyxoviruses, Nipah virus is readily inactivated by soaps, detergents and many disinfectants. Routine cleaning and disinfection with sodium hypochlorite or commercially available disinfectants is expected to be effective. Sodium hypochlorite was recommended for the disinfection of pig farms in Malaysia.

The effect of heat may depend on the substrate. Nipah virus concentrations decreased but the virus was not completely eliminated in artificial palm sap held at 70°C for 1 hour. However, it was completely inactivated by heating at 100°C for more than 15 minutes.

Infections in Animals

Incubation Period

The incubation period in pigs is estimated to be 7 to 14 days, but it may be as short as four days. Experimentally infected cats developed clinical signs after 6-8 days and experimentally infected ferrets after 6-10 days.

Clinical Signs

Pigs

Subclinical infections appear to be common in pigs. Symptomatic infections are usually acute febrile illnesses, but fulminating infections and sudden death have also been seen. In general, mortality is low except in young piglets.

A respiratory syndrome appears to be the most common presentation in 1-6 month old pigs, with clinical signs that may include fever, nasal discharge, open-mouthed breathing, rapid and labored respiration and a loud barking cough. Hemoptysis can occur in severe cases. Pigs in this age group occasionally develop neurological signs such as trembling, twitching, muscle spasms, myoclonus, weakness in the hind legs, spastic paresis, lameness, an uncoordinated gait when they are driven or hurried, and generalized pain that is particularly evident in the hindquarters. One experiment suggested that bacterial meningitis might be a contributing factor in some animals, especially when the neurological signs develop later in the course of the disease.

Similar clinical signs can occur in sows and boars, although neurological signs appear to be more common in sows than younger animals. Reported signs in these pigs include agitation, head pressing, nystagmus, chomping of the mouth, tetanus-like spasms, seizures and apparent pharyngeal muscle paralysis. Some sows aborted during Nipah virus outbreaks, generally during the first trimester. Sudden death may also be seen.

In piglets, common signs include open-mouthed breathing, leg weakness with muscle tremors, and twitching. Deaths may also occur due to starvation if the dam is ill.

Other species

Horses thought to be infected with Nipah virus in the Philippines either developed acute, fatal neurological signs or died suddenly with no apparent preceding illness. Although significant numbers of dogs and cats may have been infected on farms in Malaysia, clinical cases have been published for only two dogs. One of these animals had died of the illness, and the clinical signs were not described. In the other dog, the disease resembled canine distemper; the clinical signs included fever, respiratory distress, conjunctivitis, and mucopurulent nasal and conjunctival discharges. Experimental inoculation of cats with Nipah virus resulted in severe respiratory signs with fever, depression, an increased respiratory rate and dyspnea. Three cats thought to have been infected during an outbreak in the Philippines were found dead, while a fourth was moribund with terminal bleeding from the nose and mouth.

Experimentally infected ferrets developed severe depression, serous nasal discharge, coughing, dyspnea, tremors and hindlimb paresis. Neurological and/or respiratory signs, which can be severe, have also been reported in some experimentally infected hamsters.

An unproductive cough, poor growth, severe respiratory signs and deaths were documented in naturally infected goats in Malaysia. Two goats associated with a Nipah case in Bangladesh had a febrile neurological syndrome, but whether their illness was caused by Nipah virus or another disease is unknown.

Infections in fruit bats appear to be asymptomatic.

Post Mortem Lesions

In pigs, lesions may be found in the lungs, brain or both organs. Lung lesions range from mild to severe, and can include varying degrees of consolidation, petechial or ecchymotic hemorrhages, and emphysema. On cut surface, the interlobular septa may be distended. The bronchi and trachea may contain frothy, sometimes bloodstained, fluid. In the brain, there may be congestion of the cerebral blood vessels and meningeal edema. Mottled, enlarged and congested lymph nodes were also reported in some experimentally infected pigs. The kidneys may be congested with petechiae in the renal capsule and cortex, but are often normal.

In dogs, necropsy lesions have been reported only for two animals. In one dog, diffuse red-pink mottling and consolidation were seen in the lungs, with exudates in the bronchi and trachea. The visceral pleura were yellowish-cream and opaque. Irregular reddening was noted in the renal capsules and cortices. In addition, nonsuppurative meningitis, signs of cerebral and hepatic vascular degeneration, and necrosis and inflammation of the adrenal gland were seen. Similar lesions were reported in the other dog, although there was severe autolysis.

Lesions in experimentally infected cats included hydrothorax, consolidation and edema in the lungs, edema of the pulmonary lymph nodes and froth in the bronchi. Meningitis was reported in some cats after histopathological examination. More subtle lesions were seen in earlier stages of the disease; they included numerous small hemorrhagic nodules in the lungs, scattered hemorrhagic nodules on the visceral pleura, and, in one cat, edema of the bladder serosa with dilation of the serosal lymphatic vessels. Generalized vasculitis was seen in one naturally infected cat in Malaysia, particularly in the brain, kidney, liver and, to a lesser extent, the lung.

Nonsuppurative meningitis was reported in an infected horse in Malaysia.

Diagnostic Tests

Nipah virus infections can be diagnosed by virus isolation, the detection of antigens or nucleic acids, and serology. Histopathology also aids diagnosis. In swine, Nipah virus has been detected in respiratory secretions, blood and

various tissues including the bronchial and submandibular lymph nodes, lung, spleen, kidney and brain. In experimentally infected cats, this virus has been found in the lung and spleen, and less often, in the kidney, lymph nodes and other organs. It can also be detected in feline blood, urine and respiratory secretions. In dogs, viral antigens or RNA have been found in the brain, lung, spleen, kidney, adrenal gland and liver. Stringent precautions should be used to protect people when collecting samples from animals. Standardized sampling procedures, including limited sampling techniques to help safeguard personnel (e.g., 'keyhole' sampling of target tissues such as lung and lymph nodes), have been published for the closely related Hendra virus, but do not appear to be available for Nipah virus.

Reverse transcription-polymerase chain reaction (RT-PCR) assays on blood, secretions, excretions or tissue samples can be used for a rapid diagnosis. Virus isolation is available in a limited number of laboratories, as Nipah virus is a BSL4 pathogen and must be cultured under high-security conditions. This virus is often isolated in Vero cells, but many other cell lines (e.g., RK-13, BHK and porcine spleen cells) can also be used. Nipah virus can be cultured in embryonated chicken eggs; however, this system is not generally employed due to the ease of culture in cells. Isolated viruses can be identified by methods such as RT-PCR, immunostaining or virus neutralization. Electron or immunoelectron microscopy may also be helpful. Molecular methods (e.g., RT-PCR), comparative immunostaining or differential neutralization assays can distinguish Hendra and Nipah viruses. Viral antigens can be detected directly in tissues with immunoperoxidase or immunofluorescence assays.

Serology can be helpful, especially in pigs, which are often infected subclinically. Both virus neutralization and ELISAs have been used in animals. Nipah virus can cross-react with Hendra virus and other henipaviruses in these assays. These reactions can be distinguished with comparative neutralization tests.

Treatment

No specific antiviral treatment is available for Nipah virus. Infected animals have generally been killed to prevent the virus from being transmitted to human caretakers.

Control

Disease reporting

Veterinarians who encounter or suspect a Nipah virus infection should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal veterinary authorities should be informed immediately.

Prevention

Good biosecurity is important in preventing infections on pig farms; strategies should target routes of contact with other pigs as well as fruit bats. Fruit tree plantations should be removed from areas where pigs are kept. Wire screens can help prevent contact with bats when pigs are raised in open-

sided pig sheds. Run-off from the roof should be prevented from entering pig pens. Fruits that may have been contaminated by bats should not be fed to pigs or other livestock. Feeding spoiled or contaminated date palm sap to livestock, as is sometimes done in endemic areas, also appears to be a dangerous practice.

Early recognition of infected pigs can help protect other animals and humans. Due to the highly contagious nature of the virus in swine populations, mass culling of seropositive animals may be necessary. Quarantines are also important in containing an outbreak; in Malaysia, Nipah virus mainly seemed to spread between farms in infected pigs. Fomites and equipment should be cleaned and disinfected. Other animals, including dogs and cats, should be prevented from contacting infected pigs or roaming between farms. No vaccines are currently available for any species.

Morbidity and Mortality

There are few studies on the epidemiology of Nipah virus infections in flying foxes. Studies from Malaysia reported that 9-17% of *Pteropus vampyrus* and 21-27% of *P. hypomelanus* had antibodies to this virus; however, the frequency and timing of virus shedding in bats is unknown. Some studies have suggested that it may be uncommon and/or intermittent.

Nipah virus was widespread in pigs during the 1998-1999 outbreak in Malaysia. Before this virus was eradicated from domesticated swine, seropositive animals were found on approximately 5.6% of all pig farms. On one farm, more than 95% of all sows and 90% of the piglets had antibodies to this virus. The morbidity rate is estimated to approach 70-100%, but the mortality rate is low (e.g., 1-5% in 1-6 month old pigs) except in piglets. Mortality in the latter age group was approximately 40% in Malaysia, although neglect of the piglets by sick sows may have also played a role.

The frequency of Nipah virus infections in other species is unknown, although other domesticated animals were infected from pigs during outbreaks in Malaysia. While clinical cases were only confirmed in two dogs, a number of dogs are said to have died on infected farms. Farmers also reported illnesses in cats and goats. Serological surveys found seroprevalence rates of 15%-55% in dogs, 4%-6% in cats, and 1.5% in goats in the outbreak area. Infections in horses seemed to be rare during this outbreak: only five horses out of more than 3200 were positive by serology, and viral antigens were found in a single horse that died with signs of meningitis. Direct bat to animal transmission might be uncommon. In 2004, no feral cats living near an infected bat colony on Tioman Island, Malaysia had antibodies to Nipah virus.

There have apparently been no significant outbreaks among domesticated animals during human outbreaks in Bangladesh and India, and there are no published reports of proven cases in animals from this region. Whether this is due to little or no virus transmission to these animals, or limited surveillance and diagnostics is unclear. A recent human

outbreak in the Philippines was linked to contact with sick horses, although it could not be confirmed that the horses were infected (no tissues were available). Four cats and one dog died soon after eating tissues from sick horses during this outbreak. Antibodies to Nipah virus were detected in dogs but not cats in the area.

Infections in Humans

Incubation Period

Clinical cases in humans usually become apparent several days to 14 days after exposure; however, incubation periods as short as 2 days or as long as a month or more have been reported. Some people with mild or subclinical infections can develop late-onset encephalitis months or years later. One such case occurred after 11 years.

Clinical Signs

Although some Nipah virus infections can be asymptomatic or mild, most recognized clinical cases have been characterized by respiratory disease and/or acute neurological signs. The initial symptoms are flu-like, with fever, headache, sore throat and myalgia. Nausea, vomiting and a nonproductive cough may also be seen. This prodromal syndrome may be followed by encephalitis, with symptoms such as drowsiness, disorientation, signs of brainstem dysfunction, convulsions, coma and other signs. Segmental myoclonus was common in patients with encephalitis in Malaysia, and cases of meningitis, as well as encephalitis, were documented in the Philippines. Nipah virus infections in some patients appear as respiratory disease, including atypical pneumonia or acute respiratory distress syndrome. These patients may or may not develop neurological signs. Septicemia, bleeding from the gastrointestinal tract, renal impairment and other complications are possible in severely ill patients. Survivors of encephalitis may have mild to severe residual neurological deficits, or remain in a vegetative state.

Some people infected with Nipah virus develop relapsed encephalitis or late-onset encephalitis, months or years later. The latter syndrome occurs in a person who was initially asymptomatic or had a non-neurological illness. The clinical signs usually develop acutely, with symptoms that may include fever, headache, seizures and focal neurological signs. Some cases are fatal.

Diagnostic Tests

Nipah virus infections in people can be diagnosed by virus isolation, serology and RT-PCR, as in animals. In humans, this virus has been isolated from blood, throat or nasal swabs, cerebrospinal fluid (CSF) and urine samples, as well as from a variety of postmortem tissues. It is most likely to be recovered from clinical samples early in the illness, and virus isolation from the CSF is a poor prognostic sign. In patients who have died, immunohistochemistry can also be used to detect viral antigens in tissues. Nipah virus antigens are most

likely to be found in the central nervous system (CNS), followed by the lung or kidney.

Serological tests used in humans include ELISAs to detect henipavirus-specific IgM or IgG, and serum neutralization. Antibodies to Nipah virus occur in serum and/or CSF. IgM can be found in a significant number of patients during the illness. A rising titer, using acute and convalescent sera, is also diagnostic.

Treatment

Treatment is supportive, with some patients requiring measures such as mechanical ventilation. Ribavirin appeared to be promising in some outbreaks, but had little or no effect on the outcome in animal models, and its efficacy is currently considered to be uncertain. Other potential treatments, such as the administration of antibodies to Nipah virus, are being investigated in preclinical studies.

Control

Pigs seem to be important amplifying hosts for Nipah virus, and preventing infections in this species can decrease the risk of infection for humans. Sick animals should not be used for food, even if the meat is to be cooked, as the slaughter process can increase human exposure to viruses in the tissues. Close contact with fruit bats and their secretions and excretions should also be avoided. Bats have been observed visiting date palm sap collection sites at night, and can contaminate collection pots with urine and saliva. While the general recommendation is to avoid drinking any unpasteurized juices in endemic regions, keeping bats away from sap collection sites with protective coverings (e.g., bamboo sap skirts) may be helpful in areas where people are unlikely to stop drinking raw date palm sap. Smearing lime on the collection area to discourage bats appeared to have little inhibitory effect in one study. Fruit should be washed thoroughly, peeled or cooked before eating. Good personal hygiene, including hand washing, is likely to reduce the risk of infection from the environment.

Nipah virus has been classified as a Hazard Group 4/BSL4 pathogen; infected animals, body fluids and tissue samples must be handled with appropriate biosecurity precautions. People who come in close contact with potentially infected animals should wear protective clothing, impermeable gloves, masks, goggles and boots. Because Nipah virus can be transmitted from person to person, barrier nursing should be used when caring for infected patients. Patients should be isolated, and personal protective equipment such as protective clothing, gloves and masks should be used. Good hygiene and sanitation are important; in one study, hand washing helped prevent disease transmission. Vaccines are currently not available for humans.

Morbidity and Mortality

Nipah virus has emerged repeatedly into humans in Southeast Asia, with more than 500 cases identified as of 2016. The first known cases occurred in Malaysia (and

abattoir workers in Singapore) in 1998-1999, although retrospective diagnosis shows that human infections also occurred in 1997. Approximately 283 cases of encephalitis (including late onset cases) were reported in Malaysia during these outbreaks, with 109 deaths. Most people were infected by contact with pigs, and human cases were not seen after seropositive animals had been culled. However, sporadic cases and clusters have been reported most years from Bangladesh, and occasionally from India, since 2001. These infections tend to be clustered in certain regions, although isolated cases have been reported from other areas. Outbreaks in Bangladesh are seasonal and occur mainly between December and May, which is also the period when date palm sap is harvested. Drinking raw date palm sap is thought to be responsible for a number of cases, but person-to-person transmission is also significant, and nosocomial outbreaks have occurred in hospitals where barrier nursing precautions were inadequate. Additional routes of exposure, such as contact with bat excretions when climbing trees, have been suspected in some cases.

Serological studies suggest that some human infections may be asymptomatic or mild, although the prevalence of such cases is currently unclear. In the Malaysian outbreak, the subclinical infection rate was estimated to be 8-15%. In clinical cases, the fatality rate has ranged from 38% to approximately 70-75% in various outbreaks, with higher rates reported from some small case series. The case fatality rate is reported to be much higher in Bangladesh and India than Malaysia, but whether this is due to strain variability or to differences in healthcare is uncertain. One study reported a higher mortality rate in people with diabetes. Among surviving patients, an estimated 19-32% have residual neurological deficits, and higher rates have been reported in patients with more severe neurological signs. In Malaysia, late onset or relapsed encephalitis occurred in <5% and < 10% of patients, respectively, with an overall case fatality rate of 18%.

Internet Resources

[Centers for Disease Control and Prevention. Nipah Virus](#)

[Food and Agriculture Organization of the United Nations. Manual on the Diagnosis of Nipah Virus Infection in Animals.](#)

[The Merck Veterinary Manual](#)

[WHO Emergencies preparedness, response : Nipah Virus](#)

[World Organization for Animal Health \(WOAH\)](#)

[WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals](#)

[WOAH Terrestrial Animal Health Code](#)

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