

Nipah Virus Infection

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 in fruit bats of the genus *Pteropus*, a host to which it seems well adapted. It emerges periodically to affect humans, pigs and occasionally other domesticated animals. Nipah virus infections were first described during widespread outbreaks that occurred in Malaysia in 1998-1999. The virus had apparently circulated in domesticated swine since 1996, but because the mortality rate was low and the disease resembled other porcine infections, it was not identified immediately as a new disease. The epidemic was recognized when Nipah virus spread to pig farmers and abattoir workers in Malaysia and Singapore, causing severe, often fatal encephalitis in approximately 260 people. Some other species, including cats and dogs, 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.

Since 2001, human outbreaks and clusters of cases have been reported periodically in Bangladesh and a neighboring region of northern India. In some of these outbreaks, Nipah virus seems to have been transmitted directly from bats to humans, with person-to-person transmission the most significant means of spread. Why Nipah virus periodically emerges into humans and domesticated animals is not known; however, fruit bat populations in Southeast Asia are being disrupted by various factors that may alter their foraging patterns and behavior, and bring them into closer contact with domesticated animals and humans.

Etiology

Nipah virus is a member of the genus *Henipavirus* in the family Paramyxoviridae. This genus also includes the closely related Hendra virus. Different variants of Nipah virus appear to have been involved in the various outbreaks in Malaysia, Bangladesh and India. At least two major strains of Nipah virus were isolated from pigs in Malaysia.

Geographic Distribution

Nipah virus infections have been documented in Malaysia, Bangladesh and northern India. Cases were also reported in abattoir workers in Singapore who contacted pigs imported from Malaysia. This virus has been isolated from bats in Cambodia, and seropositive and RNA-positive bats have been reported from Thailand. Although Nipah virus should be considered endemic in Southeast Asia, outbreaks seem to cluster in certain geographic areas.

Transmission

Bats of the genus *Pteropus* (fruit bats/ flying foxes) are the main reservoir hosts. Nipah virus has been found in the urine of wild *Pteropus* bats and in partially eaten fruit. In experimentally infected bats, this virus was isolated from the urine, kidney and uterus, but not from conjunctival, nasal, tonsillar or rectal swabs. 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. The route of transmission from bats to domesticated animals is uncertain, but pigs might be infected by eating fruit that has been contaminated with bat saliva or urine, by drinking contaminated water, or by eating aborted bat fetuses or birth products. Humans may also be infected from bats via contaminated fruit or juice; some infections have been linked to the consumption of unpasteurized date palm juice.

Nipah virus is highly contagious in swine, which can act as amplifying hosts. Pigs shed Nipah virus in respiratory secretions and saliva. During the Malaysian outbreak, transmission on a farm seemed to occur by aerosols and direct contact with respiratory secretions; virus spread between farms was usually associated with pig movements. Although Nipah virus has not been found to date in urine, it can occur in the kidneys, and exposure to pig urine is a risk factor for infection. Anecdotal evidence suggests that vertical transmission may occur across the placenta. Transmission in semen and iatrogenic spread by re-used needles has also been suggested.

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Other domesticated animals can be infected by contact with pigs. Experimental infections have also been established in cats by intranasal and oral inoculation. Horizontal transmission has not been demonstrated between cats but it is theoretically possible; Nipah virus has been found in feline respiratory secretions, urine, the placenta and embryonic fluids. *In utero* transmission has been demonstrated in this species. Although experimental studies have not been published in dogs, serological surveys in Malaysia suggest that the 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. Humans could theoretically be infected by contact with domesticated animals other than pigs, but this has not been demonstrated. Direct or indirect bat-to-human transmission was apparently responsible for some recent outbreaks. Ingestion of virus in contaminated, unpasteurized date palm juice may have been the source of an outbreak in Bangladesh in 2005. Person-to-person transmission has been reported after close direct contact, and appears to have been the major route of spread in some recent outbreaks. In humans, Nipah virus can be shed in upper respiratory secretions and urine.

Nipah virus may be transmitted on fomites. How long this virus can survive in the environment is unknown; however, unpublished experiments suggest that it can survive for days in fruit juice or fruit bat urine.

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.

Infections in Humans

Incubation Period

The incubation period in humans is usually 4 to 20 days; however, incubation periods as short as two days or as long as a month have been reported. Some people may remain asymptomatic during the initial infection, but develop serious neurological disease up to four years later.

Clinical Signs

Although some Nipah virus infections can be asymptomatic or mild, most recognized clinical cases present with acute neurological signs. The initial symptoms are flu-like, with high fever, headache and myalgia. In patients who develop encephalitis, the symptoms may include drowsiness, disorientation, convulsions and/or coma. Nausea and vomiting can also be seen. Less often, patients develop respiratory signs, which may include acute

respiratory distress syndrome. Septicemia, bleeding from the gastrointestinal tract, renal impairment and other complications can occur in severely ill patients. Cases that have progressed to encephalitis are often fatal. Surviving patients may have mild to severe residual neurological deficits, or remain in a vegetative state.

Patients who recover from neurologic disease may relapse with encephalitis several months to several years later. Encephalitis can also occur as long as four years or more after an asymptomatic or non-encephalitic infection.

Communicability

Nipah virus did not appear to spread from person to person during the 1998-1999 outbreak in Malaysia and Singapore; however, person-to-person transmission has been documented in some outbreaks in India and Bangladesh. Humans can shed Nipah virus in upper respiratory secretions and urine. Nosocomial transmission has been reported when adequate barrier nursing techniques were not in place.

Diagnostic Tests

In humans, Nipah virus infections can be diagnosed by virus isolation, the detection of antigens or nucleic acids, and serology. Histopathology also helps support the diagnosis.

Nipah virus can be recovered in many cell lines including Vero (African green monkey kidney), RK-13, BHK and porcine spleen cells. This virus can be identified in cultures by immunostaining or virus neutralization. Electron microscopy and immunoelectron microscopy can aid identification. In humans, Nipah 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. Nipah virus is most likely to be recovered from clinical samples early in the illness. This virus is classified as a biosafety level 4 (BSL4) pathogen, which restricts the number of laboratories able to perform virus isolation.

Viral antigens can be detected in formalin-fixed tissues by immunohistochemistry. Antigens are most likely to be found in the central nervous system (CNS), followed by the lung or kidney. Reverse transcription-polymerase chain reaction (RT-PCR) techniques are in routine use at some laboratories.

Antibodies to Nipah virus may be found in serum and/or CSF. Acute and convalescent samples are collected whenever possible. Serologic tests used in humans include enzyme-linked immunosorbent assays (ELISAs) and serum neutralization.

Treatment

Treatment is supportive, and may include mechanical ventilation. Ribavirin has been promising in some outbreaks but remains to be investigated fully.

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Prevention

Preventing infections in pigs can decrease the risk of infection for humans. In endemic areas, pigs and fruit bats should be avoided whenever possible. Unpasteurized juices should not be drunk, and fruit should be washed thoroughly, peeled or cooked. Good personal hygiene, including hand washing, also reduces the risk of infection.

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 have not been developed for humans.

Morbidity and Mortality

Nipah virus has emerged repeatedly into humans in Southeast Asia since 1997. The first cases were reported in Malaysia in 1998-1999, although retrospective diagnosis shows that human infections also occurred in 1997. Abattoir workers in Singapore who contacted imported pigs also became ill. During these outbreaks, most people were infected by contact with pigs, and human cases were not seen after seropositive animals had been culled. In contrast, some outbreaks in Bangladesh seem to be caused by direct or indirect transmission from fruit bats to humans, and may have been sustained by person-to-person transmission. These outbreaks have generally been seen from January to May, and usually occur in the same areas of the country. An outbreak in Siliguri, India in 2001 was linked to nosocomial transmission in hospitals, and ended after effective barrier nursing precautions were put in place.

Serologic studies suggest that some human infections are asymptomatic. In the Malaysian outbreak, the subclinical infection rate was estimated to be 8%-15%. The case fatality rate in the various outbreaks has varied from 33% to approximately 75%; the overall case fatality rate for all outbreaks in Bangladesh between 2001 and February 2005 is 64%. Among surviving patients, an estimated 25% have residual neurological deficits. Nearly 10% of the patients in the Malaysian outbreak had late onset encephalitis with a case fatality rate of 18%.

Infections in Animals

Species Affected

Fruit bats of the genus *Pteropus* are the main reservoir hosts. *P. hypomelanus*, the island flying fox, and

P. vampyrus, the Malayan flying fox; are thought to be the most important hosts in Malaysia. *P. lylei* may be the major host in Thailand and Cambodia. Antibodies occur in *P. giganteus* in Bangladesh. In addition, there is evidence of infection in other species of fruit bats and insectivorous bats including *Cynopterus brachyotis*, *Eonycteris spelaea* and *Scotophilus kuhlii* in Malaysia, and *Hipposideros larvatus* in Thailand. *P. poliocephalus* has been infected experimentally.

Nipah virus infections have also been reported in pigs, dogs, cats, horses and goats. Some authors have suggested that sheep may have been infected in Malaysia, but reports are conflicting. Nipah virus can be maintained in pig populations; other domesticated animals appear to be spillover hosts. Experimental infections have established in cats, pigs and golden hamsters (*Mesocricetus auratus*).

Incubation Period

The incubation period in pigs is estimated to be 7 to 14 days, but may be as short as four days. In experimentally infected cats, incubation periods of six to eight days have been reported.

Clinical Signs

Pigs

In pigs, asymptomatic infections appear to be common. 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.

In 1 to 6 month old pigs, respiratory symptoms seem to be more common than neurologic signs. The clinical signs may include fever, nasal discharge, open mouth breathing, rapid and labored respiration and a loud barking cough. Hemoptysis can occur in severe cases. Neurological signs are sometimes seen; reported symptoms include trembling, twitching, muscle spasms, myoclonus, weakness in the hind legs, spastic paresis, lameness, uncoordinated gait when driven or hurried, and generalized pain that is particularly evident in the hind quarters.

Similar symptoms occur in sows and boars, although neurologic disease appears to be more common in sows than younger animals. Neurological signs that have been reported include agitation, head pressing, nystagmus, chomping of the mouth, tetanus-like spasms, seizures and apparent pharyngeal muscle paralysis. Some sows may abort, generally during the first trimester. Sudden death may also be seen.

In piglets, common symptoms include open mouth breathing, leg weakness with muscle tremors, and twitching.

Other Species

Although significant numbers of dogs and cats may have been infected on farms in Malaysia, clinical cases

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have been published for only two dogs. One dog had died of the illness, and the symptoms are unknown. In the other dog, the disease resembled canine distemper; the clinical signs included fever, respiratory distress and conjunctivitis, with mucopurulent nasal and conjunctival discharges. Experimental inoculation of cats with Nipah virus results in severe respiratory disease with fever, depression, an increased respiratory rate and dyspnea.

An unproductive cough, poor growth, severe respiratory signs and death have been reported in naturally infected goats. Infections in fruit bats appear to be asymptomatic.

Communicability

Fruit bats shed Nipah virus in urine. This virus has also been isolated from partially eaten fruit, suggesting that it may be present in saliva. It might also occur in aborted fetuses and other birth products; Nipah virus has been found in the uterine fluids of bats, and the closely related Hendra virus occurs in uterine fluids and fetal tissues. Despite the high seroprevalence rates in some bat species, virus shedding may be sporadic.

Nipah virus is highly contagious in pigs, and it is easily spread during close contact. Pigs can shed this virus in respiratory secretions. Shedding in urine has not been ruled out. Other domesticated animals appear to be infected mainly by contact with pigs. Horizontal transmission has not been demonstrated between cats; however, it may be possible. Nipah virus has been found in respiratory secretions, urine, the placenta and embryonic fluid in experimentally infected cats.

Post Mortem Lesions

In pigs, lesions may be found in the lungs, brain or both organs. Lung lesions can be 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. The kidneys can be congested 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

histopathologic 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 a naturally infected cat, particularly in the brain, kidney, liver and, to a lesser extent, the lung.

Nonsuppurative meningitis was reported in an infected horse.

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 can be found in respiratory secretions, blood and various tissues including the 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.

Nipah virus can be isolated in many cell lines including Vero, RK-13, BHK and porcine spleen cells. This virus can also be cultured in embryonated chicken eggs, but due to the ease of culture in cells, this system is not generally used. Nipah virus can be identified in cultures by immunostaining or virus neutralization. Electron or immunoelectron microscopy can also be helpful. Nipah virus is a BSL4 pathogen and culture is conducted under high-security conditions. When Nipah virus infection is only one of many possible diagnoses, some laboratories may conduct primary virus isolation under BSL3 conditions; however, stringent precautions should be employed to protect laboratory personnel. Histological examination of tissues can help indicate whether Nipah virus is a likely diagnosis and BSL4 conditions should be used initially. Suspect cultures that develop a paramyxovirus-like cytopathic effect are generally transferred to a BSL4 laboratory.

Viral antigens can be detected by immunoperoxidase or immunofluorescence assays on formalin-fixed tissues. RT-PCR, used on either fresh or formalin-fixed tissues, is available in some laboratories. Serology can also be helpful. Serologic tests used in animals include virus neutralization and ELISAs. Cross-reactions can occur between Hendra and Nipah viruses in all serologic assays including virus neutralization; however, reactions to Nipah virus can be identified by comparative neutralization tests.

To prevent exposure of humans and domesticated animals, strict precautions should be taken during sample collection and shipping.

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Treatment

No specific treatment is available; animals with Nipah virus infections are generally slaughtered to prevent human infections.

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.

Early recognition of infected pigs prevents disease in other animals and humans. Due to the highly contagious nature of the virus, 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. Transmission on fomites is also possible; re-used vaccination needles may have contributed to the spread of the virus in Malaysia. During an outbreak, fomites and equipment should be cleaned and disinfected. In addition, dogs and cats should be prevented from contacting infected pigs or roaming between farms.

Although vaccines are not yet available, promising results were reported from one recent experiment in cats.

Morbidity and Mortality

Fruit bats (flying foxes) of the genus *Pteropus* seem to be the primary hosts for Nipah virus. Studies from Malaysia reported that 9%-17% of *Pteropus vampyrus* and 21%-27% of *P. hypomelanus* had antibodies to Nipah virus, while the seroprevalence in *Cynopterus brachyotis*, *Eonycteris spelaea* and *Scotophilus kuhlii* was 2%-5%. Illness or deaths have not been reported in any bat species.

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. The morbidity rate is estimated to approach 100%, but the mortality rate is low except in piglets. On one farm, more than 95% of all sows and 90% of the piglets were seropositive. Another study reported a 69% prevalence of sick pigs on farms in the cull area of Negri Sembilan and 73% in Selangor. The mortality rate in 1 to 6 month old pigs is approximately 1%-5%. In contrast, the mortality rate in piglets was approximately 40% in Malaysia; however, neglect by ill sows may have contributed to the high death rate.

During the Malaysian outbreaks, Nipah virus infections were reported in non-porcine species in affected regions. Although symptomatic infections were documented in only two dogs, a number of dogs are said to have died on infected farms. Farmers also reported sickness in cats. Serological surveys found seroprevalence

rates of 15%-55% in dogs, 4%-6% in cats, and 1.5% in goats. Infections in horses seem to be rare: only five horses out of more than 3200 were positive by serology, and viral antigens were found in a single horse that died with symptoms of meningitis. Infections in non-porcine species appear to be uncommon or nonexistent in the absence of infected pigs. Infections were not reported in swine or other domesticated animals during the outbreaks in Bangladesh or India. In 2004, no seropositive animals were found among feral cats living near an infected bat colony on Tioman Island, Malaysia.

Internet Resources

- Centers for Disease Control and Prevention. Hendra Virus Disease and Nipah Virus Encephalitis
<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/nipah.htm>
- Food and Agriculture Organization of the United Nations. Manual on the Diagnosis of Nipah Virus Infection in Animals.
<http://www.fao.org/DOCREP/005/AC449E/AC449E00.htm>
- Henipavirus Ecology Collaborative Research Group
<http://www.henipavirus.org>
- The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>
- World Health Organization (WHO) Nipah Virus Fact Sheet.
<http://www.who.int/mediacentre/factsheets/fs262/en/>
- WHO Epidemic and Pandemic Alert and Response: Nipah Virus
http://www.who.int/csr/don/archive/disease/nipah_virus/en/
- World Organization for Animal Health (OIE)
<http://www.oie.int>
- OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm
- OIE Terrestrial Animal Health Code
http://www.oie.int/eng/normes/mcode/A_summry.htm

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*Link defunct as of 2007