

## AN EMERGING ZONOSIS OF PUBLIC HEALTH CONCERN: A COMPREHENSIVE REVIEW ON NIPAH VIRUS INFECTION

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### ABSTRACT

Nipah virus (NiV) infection is an emerging zoonotic disease, which causes encephalitis and respiratory infections in humans with high mortality rate. Bats (*Pteropus*) are the natural hosts for Nipah virus. The infection is transmitted from bats (*Pteropus*) to pigs and from pigs to humans or human-to-human. Clinical symptoms include fever, headache, dizziness, vomiting followed by drowsiness, disorientation, mental confusion, and neurological signs that indicate acute encephalitis. Due to lack of vaccines and effective antiviral drugs, and diagnostics, NiV infection poses a serious public health concern. The knowledge and scientific information on Nipah virus infection is still unknown or relatively limited to many clinicians, and received little attention; hence this comprehensive review of Nipah virus infection is undertaken to highlight its importance and further research.

### KEYWORDS

Emerging zoonosis, Encephalitis, Nipah virus infection.

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## INTRODUCTION

Nipah virus (NiV) infection is a newly emerging zoonosis and lack of drugs and vaccines poses a serious public health concern. Due to its high mortality, NiV has been recognized as a global health problem and included in the list of epidemic threats treated as a priority in research and development activities.<sup>1,2</sup> The CDC classified NiV as category C in the classification of pathogens, and any handling has to be done in biosafety level-4 facilities.<sup>3</sup> Since the knowledge of NiV infection is still unknown or relatively limited to many clinicians, this comprehensive review of NiV infection is undertaken with an aim to discuss NiV outbreaks, transmission, clinical features, diagnosis, treatment, control and prevention measures, and for planning future control and preventive, and treatment procedures, and to highlight its importance and further research.

## DISEASE OUTBREAKS AND EPIDEMIOLOGY

Nipah virus (NiV) infection was first identified in 1998–1999 during an outbreak of encephalitis and respiratory illness among pigs and pig farmers and people with close contact with pigs in a village named Kampung Sungai Nipah in Perak state, Malaysia,<sup>4,5</sup> and reached Singapore.<sup>6</sup> The virus was named after the village Nipah (Nee-pa).<sup>4,5</sup> During this first recognized outbreak in Malaysia and Singapore, most human infections resulted from direct contact with secretions from the pigs or their contaminated tissues. The NiV strain identified in this outbreak appeared to have been transmitted initially from bats to pigs, with subsequent spread within pig populations. No occurrence of human-to-human transmission was reported in this outbreak.<sup>4,6</sup>

NiV outbreak was again identified in Meherpur District, Bangladesh in 2001. The outbreaks again appeared in 2003, 2004 and 2005 in Naogaon, Manikganj, Rajbari, Faridpur, and Tangail Districts in Bangladesh. In these outbreaks, humans became infected with NiV as a result of consuming date palm sap (toddy) that had been contaminated with urine or saliva from infected fruit bats. These outbreaks occurred almost annually from 2001 to 2013 in Bangladesh.<sup>7</sup> Genetic sequencing confirmed this virus as Nipah virus, but a strain different from the one identified in 1999 outbreak in Malaysia.<sup>8</sup>

In India, the first large outbreak<sup>9</sup> of NiV infection occurred in 2001 in Siliguri, West Bengal, with 66 cases and 45 deaths, followed by a second small outbreak<sup>10</sup> in 2007 in Nadia district, West Bengal, with five cases and 100% fatality rate. These outbreaks were across the border from Nipah belt in Bangladesh. In May, 2018, an outbreak of Nipah virus infection occurred in the Kozhikode and Mallapuram districts of Kerala state, India, mainly characterized by acute respiratory syndrome and encephalitis. There were 18 confirmed cases, 17 deaths, with highest mortality rate exceeding 90%.<sup>11-14</sup>

During the later outbreaks in Bangladesh and India, Nipah

virus spread directly from human-to-human through close contact with people's secretions and excretions.<sup>12-14</sup> In Siliguri, India in 2001, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors (Nosocomial transmission).<sup>12,13</sup>

In the majority of previous outbreaks in Bangladesh and India, the initial spillover of the virus was via contaminated food, typically date-palm sap (Toddy). To collect the sap, people shave the bark off date-palm trees so it runs into a collection pot. The sap is then either consumed fresh as a sweet drink, or allowed to ferment. Humans may become infected with Nipah virus when bats come at night to lick the trunks of the trees as the sap is flowing down and as they enjoy a sugary drink, they contaminate the sap or underlying pot with saliva or urine carrying the virus.<sup>9,15</sup> In 2014, an outbreak of NiV infection occurred in Philippines in 2014, with 17 confirmed cases and 82% case fatality rate. Ten patients had a history of close contact with horses or of horse meat consumption. Fruit bats were the most likely source of infection to horses. Five patients, including two health care personnel, acquired the disease through human-to-human transmission. This strain was closely related to the Malaysian strain where human-to-human transmission had not been identified, which suggests the co-evolution of different strains of NiV.<sup>16</sup>

In Nepal, the status of NiV infection is unknown. The fruit bats of genus *Pteropus* are present in Nepal. Health officials are put in high alert to prevent the entry of disease.

## TRANSMISSION

NiV is a zoonotic virus. Fruit bats of the family Pteropodidae—particularly species belonging to the *Pteropus* genus (otherwise called flying foxes) are the natural hosts for Nipah virus. There is no apparent disease in fruit bats. Infected fruit bats sheds virus in their saliva or urine or body secretions, which infects pigs as well as other domestic animals such as horses, goats, sheep, cats and dogs, and humans get infection by direct contact with these animals. Pigs act as amplifying host. Nipah virus can be transmitted to humans:<sup>4,6,17</sup>

1. By direct close contact with infected animals such as bats or pigs and/or humans (NiV infected people).
2. Droplet infection: by respiratory droplets, nasal or throat secretion of infected animals
3. Eating contaminated fruits and juices with body secretion of animals. Consumption of raw date palm sap (toddy) is a significant risk factor as bat excreta often contaminates date palm sap. Bats are known to drink toddy that is collected in open containers, and occasionally urinate in it, which makes it contaminated with the virus.
4. Human-to-human transmission with direct contact with infected persons, most commonly in the family and caregivers of Nipah virus-infected patients.

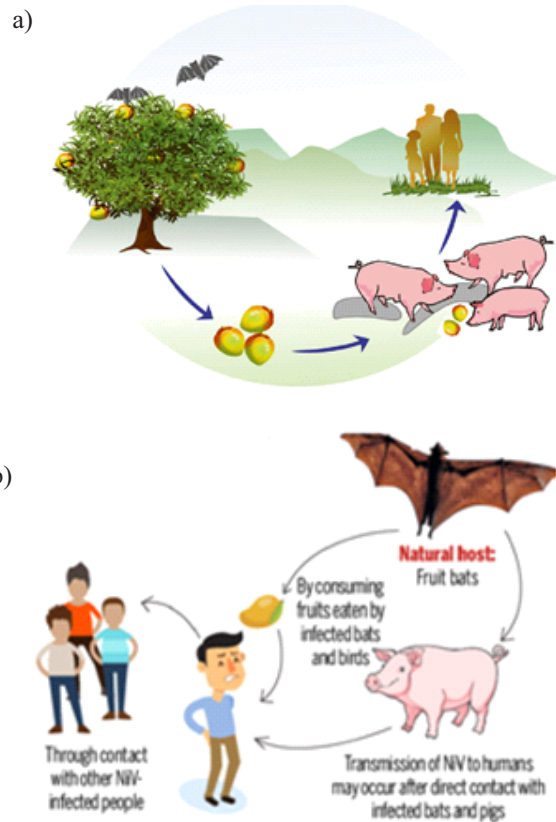


Fig 1. Transmission of Nipha virus<sup>17</sup>

a) bat-to-pig, pig-to-human

b) bat-to-human, human-to-human

**VIROLOGY**

Nipah virus (NiV) is a RNA virus, a member of the family Paramyxoviridae (Order Mononegavirales), genus *Henipavirus* and is related to Hendra virus that infects horses. Nipah virus is an enveloped virus measuring 40 to 600 nm in size and pleomorphic. Nipah virus genome is non-segmented, single-stranded negative-sense RNA, with 18.2 kb length, and contain six genes corresponding to six structural proteins. They are nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G) and polymerase (L). F and G proteins are responsible for adhesion and penetration of virus to host cell.<sup>18</sup> Phosphoprotein (P) gene codes for the synthesis of accessory virulence factors known as C, V, and W.<sup>19</sup>

Two different strains of NiV have been reported according the differences in viral properties; the Malaysian NiV strain (NiV<sub>M</sub>) closely similar to *Henipavirus* genus, and Bangladeshi NiV strain (NiV<sub>B</sub>). NiV<sub>M</sub> has no trace of human-to-human transmission, whereas NiV<sub>B</sub> can be transmitted directly human-to-human; Thus NiV<sub>B</sub> is more infectious than NiV<sub>M</sub>.<sup>20</sup>

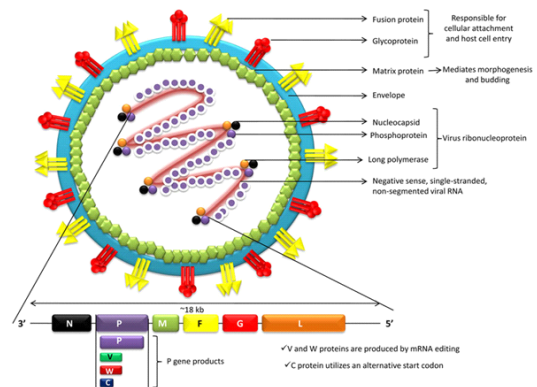


Fig 2. Structure of Nipah virus<sup>21</sup>

**PATHOGENESIS**

Incubation period in infected pig ranges from four to 14 days. Infected pigs may develop clinical symptoms such as acute respiratory and neurologic illness resulting in economic losses for farmers. Nipah viruses are believed to infect respiratory tract epithelial tissue resulting in shedding of epithelial lining along with nasopharyngeal secretion. During late stage, virus spread to lung endothelium resulting in endothelial syncytium and mural necrosis. Nipah virus can then enter the blood stream and disseminate throughout the host in either free form or by binding host leucocytes. Nipah virus has been shown to bind to CD3+ leucocytes without entry or replication of the virus. The brain, spleen and kidneys are the other target organs. Nipah virus enters into CNS via olfactory nerve and/or via the hematogenous route through the choroid plexus and cerebral blood vessels. Infection of CNS in humans is characterized by vasculitis, thrombosis, parenchymal necrosis, and presence of viral inclusion bodies. The incubation period for NiV in humans usually varies about five to 14 days. There have been a few cases with much longer incubation periods, as long as 45 days.<sup>22-26</sup>

**CLINICAL SYMPTOMS**

Clinical illness in humans range from asymptomatic subclinical infection to symptomatic acute respiratory infection (mild, severe) and fatal encephalitis (inflammation of the brain). The case fatality rate may vary between 40-70% depending on epidemiological surveillance and clinical management. Initially, infected people develop influenza like symptoms including fever, sore throat, headache, vomiting and myalgia (muscle pain). Some patients can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. This can be followed by dizziness, drowsiness, altered consciousness, disorientation, mental confusion, and neurological signs that indicate acute encephalitis. Encephalitis and seizures occur in severe cases, progressing to coma within 24-48 hours and eventually death. Most patients who survive acute encephalitis make a full recovery, but long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with long-term residual neurological sequelae such as seizure disorder and personality changes. During the Nipah virus

disease outbreak in 1998-99, about 40% of the patients who entered hospitals with serious nervous disease died. A small number of people who recover may develop latent infections with subsequent reactivation or relapse or develop delayed onset encephalitis.<sup>22-26</sup>

## LABORATORY DIAGNOSIS

Nipah virus infection can be diagnosed by virus isolation, histopathology, immunohistochemistry, serological and molecular tests.<sup>27</sup> Virus isolation from CSF, blood, nasal or throat swabs, urine, and biopsy samples in Vero cell lines is gold standard and is very helpful while determining the etiology of new outbreak. The virus produces a cytopathic effect of syncytia formation and cell death within three days.<sup>6,26</sup> The viral antigen in infected cells can be detected by immunofluorescence or antigen capture ELISA.<sup>28-32</sup> Antibody detection by ELISA (IgG and IgM) can be used later on.<sup>9,27,28,33</sup> Molecular tests like RT-PCR can be used for further identification of NiV.<sup>27,29,30</sup>

## TREATMENT

There is no specific treatment or vaccine available for Nipah virus infection. The primary treatment for humans is limited to intensive supportive care to treat severe respiratory and neurologic complications.<sup>28,34</sup>

Because Nipah virus encephalitis can be transmitted human-to-human, standard infection control practices and proper barrier nursing techniques are important in preventing nosocomial transmission.<sup>28</sup> The antiviral drugs ribavirin and acyclovir has been shown to be effective against the viruses *in vitro*, but human investigations to date have been inconclusive and the clinical usefulness of these drugs remain uncertain.<sup>28,35,36</sup> The anti-malarial drug chloroquine was shown inhibiting NiV in cell cultures, although no clinical benefit has yet been observed *in vivo*.<sup>9,30,35</sup> Passive immunization using a human monoclonal antibody targeting the viral G glycoprotein has been beneficial in human trials.<sup>37</sup>

## PREVENTION

Nipah virus infection can be prevented by avoiding exposure to sick pigs and bats in endemic areas and not drinking raw date palm sap (Toddy). Routine and thorough cleaning and disinfection of pig farms with appropriate detergents or sodium hypochlorite may be effective in preventing infection in pigs. If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals with close supervision of burial or incineration of carcasses, may be necessary to reduce the transmission of infection to people. Gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures to avoid the risk of animal-to-human transmission.<sup>9,28,38</sup>

Keeping bats away from sap collection sites with protective coverings (such as bamboo sap skirts) and other fresh food

products may be helpful in reducing the risk of bat-to-human transmission. Freshly collected date palm juice should be boiled, and fruits should be thoroughly washed and peeled before consumption. Fruits with sign of bat bites should be discarded. Using water from wells infested by bats should be avoided.<sup>9,28,35</sup>

Health care workers caring for suspected NiV patients, or handling specimens from them, should implement standard infection control precautions at all times, such as regular hand washing and disinfecting with 70% ethanol is very important to avoid the risk of human-to-human transmission. Health care workers should employ quarantine methods and use barrier methods such as gloves, masks, and disposable gowns, as they are at high risk of human-to-human transmission.<sup>28,33</sup> NiV is easily inactivated by soaps, detergents and many disinfectants.<sup>38</sup>



**Fig 2.** A date palm sap (Toddy) collector uses a bamboo skirt to cover an area of shaved bark on the tree and protect the sap from fruit bats; a method of making date palm sap safer to drink.<sup>37</sup>

A subunit vaccine, using the Hendra G protein, produces cross-protective antibodies against Hendra virus and Nipah virus has been recently used in Australia to protect horses against Hendra virus. This vaccine offers great potential for *Henipavirus* protection in humans as well.<sup>39</sup>

## CONCLUSION

Nipah virus is a highly infectious zoonotic paramyxovirus spreads by bats in humans and animals; causes encephalitis and respiratory infections in humans with high mortality rate. Due to lack of specific drugs and vaccines with proven effectiveness and diagnostic tests is of serious public health concern.<sup>40</sup> Any zoonotic virus, with the ability to human-to-human transmission, can be very dangerous and explode as global pandemic. Drawing conclusions from the COVID-19 pandemic we must be prepared and efforts must be focused on surveillance and awareness that will help prevent future outbreaks. Further research is needed to develop vaccines and drugs for the prevention and treatment of NiV infection and to control future outbreaks.<sup>39,40</sup>

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