


LITERATURE REVIEW

Received: 03 March 2026
Last revision: 29 March 2026
Accepted: 31 March 2026
Published: 18 September 2026

Nipah Virus Infection: A Narrative Review

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ABSTRACT

Nipah virus (NiV) infection is a zoonotic disease causing recurring outbreaks since 1998. Nipah virus is highly contagious, responsible for high morbidity and mortality, and has the potential to become a pandemic. World Health Organization (WHO) has put this zoonotic disease on its priority pathogen list. Nipah virus can be transmitted to humans directly from bats or through an intermediary animal. It primarily affects the respiratory system and central nervous system acutely and is rapidly progressive. The case fatality rate of Nipah virus infection is high, ranging from 40% to 75%. Nipah virus infection causes acute, rapidly progressing problems, particularly in the respiratory system and the central nervous system. Within 6 months after acute infection, some cases have persistent neurological and psychiatric symptoms, which include fatigue, neurological problems, and depression. To date, no clinically approved antivirals and vaccines are available to treat NiV infection to date. This narrative review explores the latest updates on Nipah virus infection to help prepare effective strategies to prevent transmission of the Nipah virus.

Keywords: Encephalitis, Nipah virus, outbreaks, respiratory infection, zoonotic.

https://doi.org/10.55175/cdk.v53i09.2395
e-ISSN: 2503-2720

INTRODUCTION

Nipah virus (NiV) is a zoonotic pathogen, first identified in 1998 in Sungai Nipah, Malaysia, and caused an outbreak among pig farmers in that area.[1] NiV spread quickly and caused an outbreak in 1999 in Singapore because of importation of sick pigs from Malaysia.[2] Since then, NiV has become a recurring issue, particularly in Bangladesh and India. Bangladesh has reported almost annual outbreaks since 2001. In India, outbreaks are periodically reported in several parts of the country, including the latest one in 2026.[1] In January 2026, the National IHR Focal Point for India notified two laboratory-confirmed NiV infection cases in West Bengal State. The cases were confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) and Enzyme-Linked Immunosorbent Assay (ELISA) testing. These two cases are nurses between 20 and 30 years old, and both cases developed symptoms of severe NiV infection.[3]

NiV is highly pathogenic to various mammals and can spread from person to person and animal to human (mainly by specific types of fruit bats, predominantly *Pteropus spp.).*[4] The bats can spread the virus directly to animals and humans or indirectly through contaminated saliva, urine, and feces.[4] They live in various countries of South and Southeast Asia.

It is believed that potential NiV transmission to animals and humans is linked to habitat loss for these bats. In Malaysia, the NiV is transmitted to humans through infected pigs, which act as the intermediate host of the virus.[5] In Bangladesh, NiV was transmitted to humans through the consumption of infected date palm sap.[1] Sneezing and coughing of infected individuals can spread NiV via aerosol droplets. In Bangladesh, the transmission of NiV through food and water has been identified as a significant risk factor.[5] The ability of these diseases to spread quickly leads to significant global mortality, morbidity, and economic impact.[2] Due to its outbreak potential, NiV has been classified by the World Health Organization (WHO) as a priority pathogen requiring urgent research and development.[4]

MAIN REVIEW

Definition

NiV infection is a type of zoonotic disease caused by NiV, a single-stranded RNA genome categorized under the genus Henipavirus and the Paramyxoviridae family. Other viruses of this family include measles virus, mumps virus, human parainfluenza virus, and Hendra virus (HeV).[2] NiV is significantly larger in size compared to most other paramyxoviruses, with a diameter ranging between 120 and 150 nm, approximately 17 nm in length. It is an enveloped virus with helical symmetry that contains a negative-sense, single-stranded, unsegmented RNA genome measuring about 18.2 kbp. The 3'-5' regions of the RNA genome have three non-structural and six structural proteins.[2] These include the genome codes for glycoprotein (G), fusion protein (F), nucleocapsid (N), phosphoprotein (P), matrix (M), and long polymerase (L). The P gene encodes the phosphoprotein (P) and three non-structural proteins known as C, V, and W proteins **(Figure 1)**. In some viruses of the Paramyxoviridae family, the genome encodes cell attachment proteins that can exert hemagglutination (H) and neuraminidase (N) functions. Viral RNA interacts with the N, P, and L genes to form the virus ribonucleoprotein (vRNP). Meanwhile, the F and G proteins facilitate virion attachment to the host cell and enable its entry.[2,5,6]

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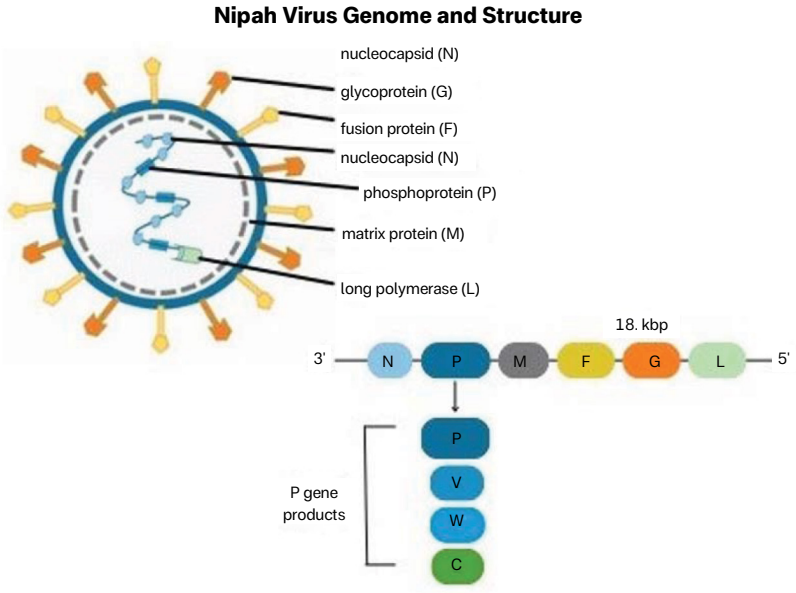

Figure 1. Nipah virus genome and structure.[5]

Fruit bats, mainly several species of Pteropus bats, are the main reservoir for some Henipaviruses. This pathogen can infect humans, pigs, horses, dogs, and cats. Non-structural proteins are essential for virulence, as they indirectly suppress the activity of immune interferons. Because of its high pathogenicity and the absence of effective treatments and vaccines, the virus is classified as a BSL-4 (biosafety level-4) pathogen. The NiV is relatively stable, remaining viable in the environment at 70 °C for 1 hour, surviving up to three days in some fruit juices, and persisting for approximately 18 hours in the urine of reservoir bats. Soaps, detergents, and common disinfectants such as sodium hypochlorite, can inactivate the virus and it is completely inactivated by heat at 100 °C for longer than 15 minutes.[5]

Pathogenesis

The NiV can infect humans through ingestion of food contaminated by bats, contact with infected animals, or body fluids from infected individuals. Human transmission occurs via two pathways: through an intermediary animal host (outbreak in Malaysia), or directly from bats to humans (outbreak in Bangladesh and India). The primary entry point is the oronasopharyngeal route.[6] High concentrations of antigen have been found in lymphoid tissue (Waldeyer's ring) and respiratory tissues, indicating that these tissues are likely the sites of initial replication.[4,5]

The NiV infection starts with the attachment of the viral G protein to the ephrin-B2 and -B3 receptors on host cells, which are present on epithelial cells, endothelial cells, and neurons. During viremia, NiV spreads in airway endothelial cells.[7,8] The NiV triggers respiratory infection through the production of inflammatory cytokines, which recruit other immune system elements, leading to a condition resembling acute respiratory distress syndrome (ARDS).

Cytokines such as interleukin IL-6, IL- 8, IL-1α, monocyte chemoattractant protein 1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF) mediate this response.[5] At the later stages, the virus spreads from the respiratory epithelium to the lung endothelial cells, targeting primarily type II pneumocytes and bronchial epithelium **(Figure 2)**.[5]

Within the first week of infection, the virus quickly spreads to various organs (kidney, heart, liver and spleen).[7] As the disease progresses, NiV disseminates into the bloodstream and infects the brain, as well as the digestive and excretory systems. The virus can access the central nervous system (CNS) through various pathways, such as replication within endothelial cells leading to blood-brain barrier (BBB) disruption; infiltration of virus-bound uninfected leukocytes and transport through olfactory neurons from the nasal cavity. The primary route is lympho-hematogenous.[6] This route modifies permeability by releasing inflammatory cytokines such as TNF-α and IL-1β, leading to the development of neurological signs.[4,5] NiV reaches the deepest part of the respiratory system by damage to pulmonary endothelial cells, so the virus can directly transmit to the nerve via the olfactory nerve **(Figure 2)**.[4,5]

A higher viral load or extended antigen exposure during acute neuroinvasive disease leads to increased immune activation, and prolonged immune stimulation may contribute to chronic neurological sequelae. Decades post-infection, IL-2-producing memory T cells remain predominant, suggesting that NiV-specific memory T cells maintain functional competence instead of entering a terminally differentiated or exhausted state. This characteristic is advantageous for vaccine-induced immunity, as IL-2 supports recall proliferation and the coordination of humoral responses.[1]

Clinical Features

The NiV induces an acute and rapidly progressing disease, primarily targeting the respiratory and CNS. Clinical symptoms typically appear 3–14 days after exposure,[2] with an incubation period ranging from 4–21 days.[9] However, in certain cases, the incubation period may extend to 4 months or longer. Latent infections have also been reported to recur several months or even years following the acute phase.[6] The clinical manifestation is marked by rapid symptom progression.[2] Initial signs often include sudden high fever, lethargy, and headache, with some patients experiencing coughing and respiratory distress. Additional symptoms may include sore throat, nausea, and myalgia. Within 24–48 hours of infection, encephalitis may develop. Common neurological manifestations include hypotonia, gaze palsy, segmental myoclonus, altered mental status, areflexia, and weakness affecting the limbs, face, eyes, hands, or whole body. In severe cases, the disease can progress to convulsions and coma **(Figure 2)**. Additionally, various clinical features are also associated with vascular and cellular damage in the brain, lungs, and kidneys. Persistent neurological and psychiatric symptoms, including

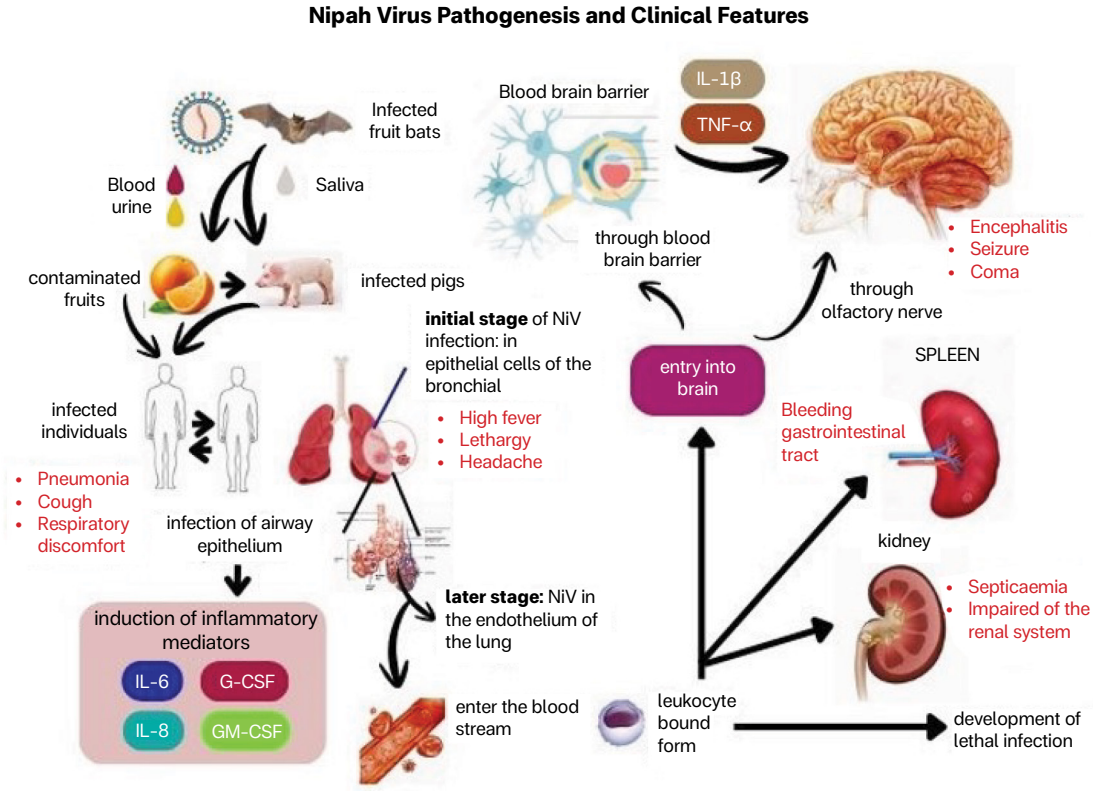

Figure 2. Nipah virus pathogenesis and clinical features. Adapted from Aditi, *et al*.,[4] and Bruno, *et al*.[5]

Abbreviations: IL: Interleukin; TNF: Tumor necrosis factor; NiV: Nipah virus; G-CSF: Granulocyte-colony stimulating factor; GM-CSF: Granulocyte macrophage-colony stimulating factor.

fatigue, localized neurological problems, and depression, have been reported from 6 months up to 10 years following acute infection. Approximately 33% of survivors with post-acute sequelae recovered within 1 year of the acute infection. Overall, the pooled prevalence of residual neurological deficits was considerable, particularly among patients who experienced encephalitis during acute infection.[10,11]

Gastrointestinal manifestations including hypersalivation and anorexia were frequently observed. Other potential complications are septicemia, renal failure, and gastrointestinal bleeding **(Figure 2)**. Histopathological analyses conducted in multiple studies further identified meningitis, interstitial pneumonia, and pulmonary edema, in addition to the clinical symptoms.[6]

Diagnosis

Early diagnosis is crucial for NiV infection due to its high case fatality rate.[6] NiV can be detected using RT-PCR, which is considered the preferred diagnostic method because of its high sensitivity, accuracy, and rapid results. During the acute phase, RT-PCR can be performed on cerebrospinal fluid (CSF), blood, nasal or throat swabs, tissue samples, and urine. Proper sample collection and handling are essential, including the use of triple container packing and storage at 2–8°C. The samples intended for storage beyond 48 hours should be kept at -20°C.[4] Genetic mutations in NiV may reduce test sensitivity by altering conserved sequences used for probe design, potentially resulting in the emergence of novel variants.[6]

The integration of the CRISPR/Cas technique with isothermal amplification assays such as RPA (Recombinase Polymerase Amplification) has facilitated the development of innovative viral diagnostic tests. Recently, in 2024, researchers in China reported a novel method that exploits the DNase activity of the Cas12a protein to target the highly conserved N gene of NiV. These diagnostic methods offer safer and more cost-effective alternatives to conventional PCR, as they do not require expensive thermal cyclers.[6]

Serological assays, like Enzyme-linked Immunosorbent Assay (ELISA), are widely used due to their high accuracy, speed, ease of use, and safety. ELISA test is developed for detecting IgG and IgM, which are used to confirm diagnosis.[4] IgM antibodies are among the first to appear during infection, usually detectable within the first 5 days of symptoms, and last for up to 90 days before eventually disappearing. IgG generally reach its highest level between 2 and 4 weeks after symptoms begin and may persist for several months to years. IgM ELISA is primarily used to detect recent or acute infections, whereas IgG tests are commonly used in serosurveillance studies, where a positive IgG ELISA indicates the convalescence phase in recovered patients.[6,12]

Detection of NiV infection can also be performed using immunohistochemistry (IHC) with formalin-fixed tissue specimens. As viral replication occurs within vascular endothelial cells, samples from organs such as the brain, lung, spleen, kidney, and lymph nodes are suitable for analysis. Early

studies using convalescent human serum for IHC demonstrated the presence of NiV antigens in renal and respiratory epithelium, smooth muscle cells, and additional tissue sites including Schwann cells in the spleen, laryngeal epithelial cells, and endothelial cells of heart valves.[6]

Differential diagnosis

Other potential causes to be considered include sporadic viral infections, such as varicella zoster virus (VZV), herpes simplex virus (HSV), enteroviruses, and adenovirus, as well as epidemic viral infections like dengue virus, Japanese encephalitis virus (JEV), and rabies virus. Bacterial infections such as rickettsial diseases, bacterial abscess, tuberculosis, and parasitic infections such as cerebral malaria should also be considered.[13]

Treatment

Despite ongoing research efforts, no drugs or vaccines have been approved yet for specific treatment of this highly important and potentially life-threatening illness. After NiV infection is detected, key clinical management strategies include maintaining respiratory function, minimizing risk of venous thrombosis, and preserving fluid and electrolyte balance. In addition, broad-spectrum antibiotics are also administered to NiV-infected patient. Patients with severe and acute respiratory failure may require mechanical ventilation support.[6]

During previous outbreaks, ribavirin, remdesivir, and acyclovir have been used as treatment options for NiV infection, although their efficacy is still unknown.[6] In the 1998 Malaysian outbreak, ribavirin was administered either orally or intravenously to patients with NiV encephalitis, leading to a reduction in mortality of up to 36%.[14] Immunotherapy has also been proposed as a potential treatment, but it is still under investigation.[6]

Various approaches have been proposed to develop vaccines against NiV, such as subunit vaccines derived from the NiV G glycoprotein (sG) and virus vector based recombinant vaccines.[4,6] In animal models, these approaches have demonstrated complete protection against oro-nasal NiV challenge after a single dose.[4,6] These vaccine candidates are currently under consideration for human use.[4]

Staying away from pigs or farm animals and avoiding raw date palm sap can reduce the chance of NiV infection. To reduce the risk of animal-to-human transmission, it is recommended that protective clothing and gloves be used while handling animals. Personal protective equipment is recommended for medical professionals during NiV treatment. Appropriate isolation, quarantine, and disinfection protocols should be implemented to enable a rapid response when a new case is identified.[4]

Prognosis

The case fatality ratio (CFR) in outbreaks ranges from 40% to 75%, indicating its severity.[3] During the outbreak in Malaysia, several factors were identified as having a poor prognosis, including advanced age, severe brain-stem involvement, comorbidities, thrombocytopenia, elevated aminotransferase, and seizures. It commonly manifests as decreased consciousness, vomiting, abnormal doll's-eye reflex, abnormal pupillary responses, hypertension, and tachycardia during disease progression. These conditions give a clearer picture of the symptoms and outcomes of this particular condition.[15]

CONCLUSION

Nipah virus infection represents an emerging zoonotic disease that contributes to high mortality, morbidity, and significant economic burden worldwide. NiV spread quickly from person to person and animals (predominantly fruit bats *Pteropus spp.*) to humans, directly or indirectly through contaminated saliva, urine, and feces. The oronasopharyngeal route is the main pathway through which NiV enters the host. The clinical manifestation of NiV infection is marked by rapid symptom progression, predominantly affecting the respiratory system and CNS. Within 6 months after acute infection, some cases have persistent neurological and psychiatric symptoms. NiV infection can be diagnosed through RT-PCR, ELISA, RPA, and IHC. Unfortunately, there are no approved drug and vaccines options for NiV infection until now for NiV infection. Therefore, the best way to control outbreaks is through surveillance and preventive measures. To ensure a rapid response to newly identified cases, it is critical to implement proper isolation, quarantine, and disinfection protocols, supported by adequate infrastructure and trained personnel equipped with protective clothing.

Funding

This manuscript received no financial support or funding.

Author Contributions

Melany Intan contributed to conceptualization, writing - original draft, visualization.
Velma Herwanto contributed to supervision, writing - review and editing.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Declaration on the Use of Artificial Intelligence (AI)

The authors declare that no artificial intelligence tools were used in the conduct of this study or preparation of this manuscript.

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