Editorial

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Nipah virus transmission: a persistent threat to public health demanding rapid diagnosis, innovative therapeutics, vigilance, and research progress

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In modern times, there has been a notable increase in various infectious diseases in many regions worldwide. The Nipah virus (NiV) is one of the emerging viruses that is responsible not only for severe respiratory problems in humans but also for deadly encephalitis. This infection has been linked to several different symptoms, such as fevers, lung problems, coughing, and others. According to WHO, it is estimated that the fatality rate of the NiV is 40–75%. NiV transmits either directly from infected reservoirs or indirectly from positive patients to others by close contact. This negative sense of bat-borne, zoonotic nature belongs to the *Henipavirus* genus, *Paramyxovirinae* subfamily, *Paramyxoviridae* family, and order *Mononegavirales*. To detect this virus, real-time polymerase chain reaction (RT-PCR) can be used from patients' nasopharyngeal or oropharyngeal swabs, CSF (cerebrospinal fluid), urine, and serum samples. Currently, there are no targeted antiviral vaccines or drugs for Nipa treatment. However, research is ongoing to find advancements in therapeutic approaches, such as the utilization of ribavirin and monoclonal antibodies. Multiple proactive strategies need to be followed to control this virus. The implementation of preventive measures, such as the avoidance of contact with infected animals, could play a crucial role in mitigating the transmission of the virus. This contagious virus, Nipah, can spread from one human to another through direct contact or indirectly infected animals, specifically pigs and fruit, namely fruit bats, which also transmit this virus.

The NiV attracted global attention after the 1998–1999 outbreak that occurred in Malaysia. A total of 300 positive cases were reported, including 100 death cases[1]. It has been found that most human cases are linked to infected pigs or related animals. Subsequently, a few epidemics have occurred in Bangladesh and India[2]. Bangladesh has witnessed several cases from 4 January 2013, to 13 February 2023. Approximately 11 laboratory-confirmed positive cases and at least one susceptible case were reported from seven districts including two divisions. At least eight associated deaths were confirmed by IEDCR (Institute of Epidemiology Disease Control And Research)[3]. In the year of 2018, a devastating outbreak with 17 deaths was reported in the Kozhikode region of India. It was linked to fruit bats, which were identified from a family farm. Another outbreak took place in the Kochi district of Kerala state in 2019. Moreover, a single fatal case was confirmed by the health authority in the Kozhikode district in 2021[2]. Most recently, two fatal cases of NiV infection were detected in Kerala state in August and September of 2023[3].

NiV is pleomorphism morphologically and appears as spherical or thread-like shapes. This virus contains one non-segmented, negative-sense, single-stranded RNA genome with an ~18 kb length. It is coated with an envelope ranging from 40 to 1900 nm[4]. The RNA genome or virus ribonucleoprotein (vRNP) comprises three essential proteins such as nucleocapsid (N), phosphoprotein (P), and long polymerase (L). Additionally, there are two cellular and one entry proteins: fusion glycoprotein (F) and glycoprotein (G), along with the matrix (M) protein. Phylogenetic analysis has been instrumental in categorizing the NiV into two fundamental genotypes: NiV-Bangladesh (NiV-BD), prevalent in Bangladesh and India, and NiV-Malaysia (NiV-MY), found in Malaysia and Cambodia[4,5].

Typically, the incubation period of the NiV is 4–14 days after exposure. The illness usually presents symptoms like respiratory infections, such as coughing, sore throat, and difficulty breathing, with fever and headache. It is also observed that drowsiness, disorientation, and mental confusion commonly occur during the subsequent phase of brain swelling (encephalitis), which can rapidly progress to a coma within 24–48 h[6]. Initial symptoms can include one or more of the following: fever, headache, cough, sore throat, breathing problems, vomiting, seizures, coma, and brain swelling.

Diagnosing NiV infections involves several methods, including histopathology, serological tests, electron microscopy, immunohistochemistry, virus isolation, and PCR. The virus has evolved mechanisms to suppress host innate immunity through

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proteins like *P*/phosphoprotein, V protein, W proteins (V and W are produced by mRNA editing), and the C protein (which utilizes an alternative start codon). These proteins can hinder the communication and synthesis of interferons (IFNs), thereby impeding the cellular antiviral response[4]. Recent research has also identified tethering, an IFN-induced protein in bats, as capable of inhibiting NiV replication in fruit bats[3].

Pathogenesis of NiV involves several stages and affects various tissues and organs throughout the body. Firstly, this virus enters the human body through the respiratory tract system. It starts infection in the airway of the bronchial epithelial cells. Subsequently, the progression of infection spreads from the airway to the patients' blood vessels. Nipha virus can invade and infect the endothelial cells lining the lung's blood vessels. The virus gains access to the bloodstream, where it can disseminate freely or hitch a ride within host leukocytes, ultimately reaching critical organs such as the brain, spleen, and kidneys.

NiV could enter the central nervous system (CNS) through two primary pathways. One route involves hematogenous transmission, wherein the virus infiltrates the brain through the bloodstream. In this process, the integrity of the blood–brain barrier is compromised, allowing the virus to breach the protective barrier. Consequently, this disruption triggers the expression of inflammatory cytokines like IL-1β and tumor necrosis factor (TNF)-α within the CNS. These changes in the brain's environment ultimately led to the development of neurological symptoms in infected individuals, often of a severe nature (Fig. 1).

In the 1998 NiV outbreak in Malaysia, an open-label ribavirin therapy trial reduced the fatality rate by 36%. Ribavirin, a licensed therapy for various viral infections, has demonstrated antiviral effectiveness against a broad spectrum of RNA and some DNA viruses[8]. Specifically, ribavirin inhibits RNA replication *in vitro* against both human pathogenic viruses and NiV; this was one of the first antivirals to treat an infection caused by the NiV virus. Additionally, a human monoclonal antibody (mAb) known as m102.4, derived from a recombinant naive human phage-displayed Fab library, has proven to be the only successful post-exposure therapy against NiV infection and may soon receive authorization for use[1]. Research on m102.4 has demonstrated its ability to neutralize multiple isolates, including both Bangladeshi and Malaysian NiV strains. Several studies have suggested that soluble forms of glycoprotein (G) and ephrin-B2 are effective at inhibiting NiV envelope-mediated infection. By interfering with the virus's ability to enter host cells, these soluble proteins can potentially serve as therapeutic agents to combat NiV infections[9,10].

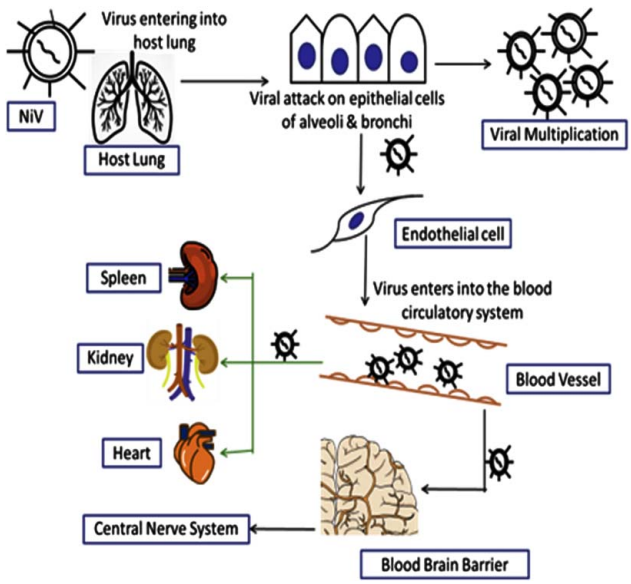

Figure 1. Pathogenesis of the Nipah virus[7].

Currently, there is no approved specific treatment for this viral disease. Despite these advances, specific medications for the treatment of NiV infection remain unapproved, and progress in developing effective therapies has been limited. Continued research and development efforts in this field are crucial to combating this significant public health threat. Nipa-affected positive patients can follow supportive care to reduce symptoms for better improvement. To solve patients' breathing issues, one may use respiratory support from ventilators or supplemental oxygen. If a patient's condition worsens, hospitalization and careful monitoring are crucial. Secondary infection treatment is also important for the patient's severity. Research and development (R&D) projects are going on to develop active vaccines and other therapeutical treatments. Although few antiviral drugs are applied in animal models including ribavirin and favipiravir, no significant study results are observed for humans. As a result, following prevention strategies are necessary to control this disease.

There is no effective prevention or cure for the NiV. Its therapy is limited to symptomatic care, hospitalization, and isolation in the absence of appropriate medications. Since there is no vaccine for the NiV, the only option to curb the spread of the sickness is to educate people and raise awareness[11].

There are several measures to prevent contracting NiV infection, including avoiding contact with infected pigs or bats in areas where the virus is prevalent and refraining from drinking raw date palm sap, which can be contaminated by bats carrying the virus. To prevent this viral disease, the use of good hygiene practices plays a significant role. Proper hand washing with soap and water or alcohol-based hand sanitizers is preferable for this virus. Further, personal protective equipment (PPE) is required for healthcare persons who handle Nipa patients. Face masks, goggles, gloves, head cover, foot cover, and protective clothing minimize transmission of this virus. One should avoid touching eyes, nose, and mouth with unwashed hands. It is recommended to visit any places where the outbreaks occurred without any reason and isolate positive patients. In places such as hospitals, infection control practices can play a crucial role in preventing the disease from spreading from person to person during an outbreak. Additionally, it is recommended to avoid planting fruit trees near piggeries that attract bats, as these trees may also attract bats carrying the virus. Wearing appropriate protective clothing is essential when engaging in work that requires direct contact with farm animals, especially during activities such as slaughtering and disposal[8]. To control this deadly disease, more studies need to be conducted, including developing new active vaccines and therapeutic treatments.

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