Overview article Pham Ngoc Thach Medical and Pharmaceutical Journal

DOI: 10.59715/pntjmp.5.2.4

Nipah Virus: From Biological Characteristics to Risk of Emergence in Vietnam

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Abstract

Nipah virus (NiV) is a high-fatality emerging pathogen that has recently continued to be recorded through clusters of encephalitis and respiratory distress in South Asia. Reports indicate that while outbreaks' scales are typically small, the virus possesses extreme virulence and the capacity for human-to-human transmission, particularly within hospital settings. Although case fatality rates reported across outbreaks range from 40% to 75%, transmission dynamics remain limited, and sustained community spread has not been observed to date. The virus is naturally harbored by fruit bats of the genus *Pteropus*, with spillover events linked to contaminated food products or intermediate hosts such as pigs; Vietnam lies within the distribution range of *Pteropus* bats, which, combined with high livestock density and rapid urbanization, creates a significant risk interface between animals and humans. International trade connectivity further increases the potential for introduction and spread of Nipah virus before being detected. This review aims to synthesize biological mechanisms, transmission dynamics, and Vietnam-specific ecological and livestock risk factors to inform preparedness strategies and public health policy.

Keywords: Nipah virus; Zoonotic spillover; Human-to-human transmission; Emerging infectious disease; One Health

Received: 20/02/2026
Revised: 20/03/2026
Accepted: 20/04/2026

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1. INTRODUCTION OF NIPAH VIRUS: DISCOVERY AND OUTBREAKS

The discovery of NiV illustrated how epidemiological analysis proved decisive when clinical presentation was initially misleading. During the 1998–1999 outbreak in Malaysia, pig farmers in Perak, Negeri Sembilan, and Selangor developed severe encephalitis and respiratory illness [1]. The disease was initially attributed to Japanese encephalitis, but this assumption was challenged when mosquito control and vaccination failed to curb cases [2], and infections clustered almost exclusively among individuals in close contact with pigs rather than following the typical mosquito-borne pattern [3,4]. The mismatch between expected transmission dynamics and observed case distribution prompted further investigation.

In 1999, Chua and colleagues isolated a novel virus from the cerebrospinal fluid of a fatal case in Kampung Sungai Nipah [1]. The agent produced rapid cytopathic effects with multinucleated syncytia *in Vero* cells and showed ultrastructural features of the family Paramyxoviridae, initially being described as a "Hendra-like virus" [2]. Concurrent cases among abattoir workers in Singapore linked to imported Malaysian

pigs further confirmed the role of pigs as intermediate hosts and occupational exposure as the main transmission route [3].

From 2001 onward, outbreaks in Bangladesh and India revealed a different pattern. In Bangladesh, transmission was linked to consumption of fresh date palm sap contaminated by fruit bats of the genus *Pteropus* [5], whereas in India, particularly since the Siliguri outbreak in 2001 and later events in Kerala, sustained human-to-human transmission including nosocomial spread was documented [6]. These shifts underscore that the epidemiology of NiV varies with ecological and social context, and that accurate identification of transmission pathways depends on rigorous field investigation rather than clinical resemblance alone.

2. PATHOMECHANISM OF NIPAH VIRUS

NiV is an enveloped, pleomorphic virus typically ranging from 100–600 nm in diameter, although larger filamentous forms have been described. Its lipid envelope contains two surface glycoproteins, G and F: G mediates attachment to the host cell receptors Ephrin-B2 and Ephrin-B3, while F, activated in a G-dependent manner, drives membrane fusion and viral genome entry [4]. Beneath the envelope, the matrix (M) protein coordinates virion assembly and budding, and the ribonucleoprotein core—composed of genomic RNA complexed with N, P, and L proteins—forms the functional replication–transcription machinery [4]. This structural integration underlies efficient entry and sustained intracellular replication.

The genome is a non-segmented, negative-sense RNA of approximately 18.2 kb arranged 3’-N-P-M-F-G-L-5’ [4]. In addition to the P protein, the P gene generates non-structural proteins C, V, and W through RNA editing or alternative reading frames [4]. V and W antagonize type I interferon responses by disrupting STAT1/STAT2 signaling within the JAK–STAT pathway, thereby creating a permissive window for viral replication. Animal models further clarify pathogenic mechanisms: African green monkeys closely reproduce human respiratory and neurological disease; Syrian hamsters demonstrate rapid neuroinvasion via the olfactory route [7]; and interferon receptor–deficient mice develop fatal encephalitis, underscoring the central role of innate immunity in viral control.

Two genetic lineages, NiV-M and NiV-B, differ by minor genomic variations, including a six-nucleotide difference, yet display distinct epidemiological and clinical patterns. NiV-B has been associated with outbreak-based case fatality rates frequently exceeding 70%, whereas NiV-M demonstrated mortality of approximately 40% during the Malaysian outbreak [1]. Clinical presentation ranges from asymptomatic infection to encephalitis and acute respiratory distress, with fever present in 99–100% of cases in pooled analyses [8]. NiV-M predominantly manifests as encephalitic disease with limited respiratory involvement, whereas NiV-B frequently combines severe neurological and respiratory syndromes, with higher rates of cough, dyspnea, and progression to ARDS [8]. The incubation period and time to death are shorter in NiV-B [8]. In addition, NiV-B has been associated with higher viral loads in respiratory secretions, which may contribute to its increased transmission in outbreak settings [8].

Pathogenesis reflects marked endotheliotropism and neurotropism mediated by Ephrin-B2/B3 distribution. Systemic vasculitis, thrombosis, and

microinfarctions contribute to multi-organ dysfunction, while direct neural invasion produces rapidly progressive necrotizing encephalitis [8]. Imaging abnormalities are common, with chest radiographs abnormal in over 80% of respiratory cases and multifocal MRI brain lesions in approximately 71% of encephalitis patients [8]. Pooled case fatality rates range from 61% to over 80% depending on lineage and healthcare access [9].

Among survivors, 22–45% experienced persistent neurological deficits, including motor impairment, seizures, cognitive decline, and psychiatric disturbances. Relapsed or late-onset encephalitis occurs in a minority of cases, even years after initial infection. Sequelae result from combined endothelial injury, neuronal apoptosis, and inflammatory cytokine–mediated secondary damage [10], while potential viral persistence within immune-privileged neural tissue may enable reactivation. Collectively, efficient immune evasion, multi-organ pathology, and documented human-to-human transmission—particularly in NiV-B—define NiV as a highly virulent pathogen with substantial outbreak potential [9].

3. MODE OF TRANSMISSION

In natural reservoirs—fruit bats of the genus *Pteropus*—NiV persists in an asymptomatic state. Experimental data indicate that infected bats show no overt clinical disease, consistent with long-term virus–host co-evolution. Viral replication remains low, with intermittent shedding through saliva, urine, feces, and semen. Shedding can increase during physiological stress such as breeding seasons or food scarcity, thereby elevating the likelihood of spillover to domestic animals such as pigs and, subsequently, to humans [11]. In this host, the virus maintains genomic stability and long-term transmission rather than inducing acute pathology.

In intermediate hosts, particularly pigs, viral behavior shifts markedly. During the Malaysian outbreaks, pigs served as amplifying hosts for the NiV-M lineage. Infection produced respiratory disease and encephalitis, with relatively low mortality in adults but higher rates in piglets [12]. Despite modest mortality among adult pigs, viral loads in respiratory secretions and urine were sufficient for efficient transmission to humans in close contact [10]. This amplification transformed a virus previously circulating silently in bat reservoirs into an outbreak-associated pathogen in humans. Additional susceptible species include horses, implicated in a Philippine outbreak with rapidly progressive neurological disease, and domestic animals such as dogs and cats, with the latter demonstrating severe respiratory and neurological involvement and possible vertical transmission, while dogs typically develop interstitial pneumonia. Such cross-species susceptibility underscores the broad host range of NiV.

In humans, NiV infection manifests as severe systemic disease. Through Ephrin-B2 and Ephrin-B3 receptors [13], the virus infects endothelial and neural cells, causing vasculitis, multi-organ injury, and necrotizing encephalitis [10]. Viral RNA has been detected in respiratory secretions, blood, cerebrospinal fluid, urine, and breast milk, reflecting widespread dissemination. Patients with prominent respiratory symptoms, particularly in NiV-B infections, exhibit higher viral shedding in the respiratory tract, facilitating human-to-human transmission. In Bangladesh and India, direct bat-to-human transmission via contaminated date palm sap or fruit is common, while secondary spread occurs through close contact.

Human-to-human transmission increases outbreak risk. Nipah virus spread occurs primarily through exposure to respiratory secretions or bodily fluids, with documented superspreading events in healthcare settings [6]. Individuals with severe respiratory involvement tend to transmit more efficiently than those with isolated neurological disease. Epidemiological contrasts between lineages are notable: NiV-M showed minimal sustained human transmission, whereas NiV-B demonstrates greater transmissibility, higher respiratory viral loads, and fatality rates frequently exceeding 70% in several outbreaks [8]. An estimated 8–9% genetic divergence may contribute to these epidemiological differences.

Current *in vitro* evidence helps explain the biological basis of this entry and spread. At the level of entry, the viral G glycoprotein binds to Ephrin-B2 and Ephrin-B3 receptors on endothelial and neuronal cells, inducing conformational changes and activating the F fusion protein [4]. The F protein then mediates the fusion process between the viral envelope and the host cell membrane, releasing the ribonucleoprotein complex into the cytoplasm. Host factors such as cortactin participate in early entry events; overexpression of cortactin reduces infection efficiency in HEK293T cells, suggesting cytoskeletal involvement. A hallmark of infection *in Vero* E6 cells is rapid syncytium formation, driven by F and G expression on infected cell membranes interacting with Ephrin receptors on adjacent cells [13]. This cell-to-cell fusion enables viral dissemination without extracellular virion release, partially evading neutralizing antibodies. Although NiV-M induces more rapid cytopathic effects *in vitro*, NiV-B causes higher mortality *in vivo*, implying that host immune dysregulation contributes substantially to disease severity [7].

Additional *in vitro* data indicate that NiV can associate with monocytes and lymphocytes, facilitating transport across endothelial barriers [7]. In blood–brain barrier models, infected immune cells traverse endothelial layers and transmit infection to neurons, providing a mechanism for rapid neuroinvasion.

Collectively, NiV employs multiple strategies: broad receptor usage enabling cross-species infection, amplification in livestock, efficient cell-to-cell fusion, respiratory shedding in severe cases, and genetic adaptability. In the setting of widespread Pteropus distribution, limited countermeasures, and global mobility, these features confer substantial outbreak potential under conducive epidemiological conditions.

4. EMERGING THREAT OF A NIPAH VIRUS PANDEMIC IN VIETNAM

Given its classification as a high-priority pathogen [14], the potential emergence of NiV in Vietnam warrants careful assessment. Vietnam lies within the distribution range of fruit bats of the genus *Pteropus*, including *P. vampyrus* and *P. lylei*, and serological evidence indicates that NiV or related viruses circulate in local bat populations [15]. The presence of natural reservoirs creates conditions for spillover, particularly as viral shedding—though typically intermittent—may increase during ecological stress.

Vietnam's high-density pig farming further elevates concern. Pigs served as efficient amplifying hosts for the NiV-M lineage during the 1998 Malaysian outbreak [1,12], and the bat–pig–human interface observed in Vietnam resembles that scenario. An initial spillover could therefore be amplified within pig populations before recognition in humans. Deforestation, agricultural expansion, and

urbanization increase wildlife–human contact, while consumption of contaminated fruit provides potential direct transmission pathways similar to those reported in South Asia [16].

Biologically, NiV retains adaptive potential as an RNA virus. The NiV-B lineage has demonstrated human-to-human transmission, including superspreading in healthcare settings, and the conserved distribution of Ephrin-B2/B3 receptors facilitates cross-species infection [13]. In a densely populated and globally connected country, imported cases could establish secondary transmission chains. Although current estimates remain below 1, if a variant were to achieve a basic reproduction number above 1, sustained community spread would become plausible.

Risk mitigation requires a One Health framework integrating medical, veterinary, and environmental surveillance. Monitoring bat and livestock populations for viral RNA and antibodies, strengthening hospital-based surveillance for acute encephalitis and unexplained respiratory distress, expanding BSL-3/4 laboratory capacity, and deploying rapid molecular diagnostics are essential. Strict infection prevention, rapid contact tracing with 21-day monitoring, and community education to reduce high-risk behaviors are equally critical. Although no licensed specific therapy exists, preparedness for investigational antivirals or monoclonal antibodies remains necessary. Overall, while ecological reservoirs, livestock density, environmental change, and viral adaptability create conditions for emergence, coordinated interdisciplinary surveillance and robust infection control can substantially reduce the likelihood of large-scale spread in Vietnam.

Clinically, early detection of high-risk pathogens like Nipath virus, not only in the severity and mortality but also in terms of transmissibility, is crucial. This is essential not only for clinical selection of appropriate targeted treatment but also for prevention. It is also of significant importance in epidemiology, as early detection of these pathogens in patients serves as an urgent warning for tracing the epidemiological source in the region aquaculture. Therefore, equipping microbiology centers and institutes in provinces and cities with real-time PCR solutions for detecting these pathogens is essential, rather than only being implemented after an outbreak has occurred. Real-time PCR testing methods and equipment are now fully feasible in most provinces and cities in Vietnam. Furthermore, the necessary materials for this test have been published in numerous international journals, and many commercial products are already available on the international market.

5. FUTURE RESEARCH

Future research and management of NiV should be grounded in a long-term, evidence-based One Health framework integrating public health, veterinary, and environmental surveillance. Ecological monitoring of *Pteropus* bat populations for viral RNA and antibodies is essential for early warning and spillover risk modeling, alongside surveillance of intermediate hosts such as pigs and horses in high-density farming areas. Strengthening farm biosecurity and studying the effects of deforestation, climate change, and urbanization on bat ecology are critical to reducing the human–wildlife interface.

In medicine, vaccine and therapeutic development remains a priority, as no licensed products are widely available. Candidates including mRNA-1215, ChAdOx1, PHV02, and Hendra G–based

subunit vaccines require continued advancement through outbreak-adapted clinical trial designs. Monoclonal antibodies such as m102.4 and Hu1F5 have shown protection in primate models, while antivirals like Remdesivir and Favipiravir need systematic evaluation in controlled trials [8]. Expanding point-of-care diagnostics and applying CRISPR-Cas and next-generation sequencing will enhance rapid detection and genomic surveillance.

Epidemiologically, strengthening syndromic surveillance for unexplained acute encephalitis and respiratory distress is vital for early outbreak detection. Evidence-based risk communication, improved infection prevention and control in hospitals, and healthcare worker training are necessary to prevent superspreading. International collaboration—including regional BSL-3/4 laboratory networks, transparent genomic data sharing, and adaptive trial platforms—remains fundamental. Sustained multidisciplinary coordination is essential to prevent NiV from escalating beyond a regional threat.

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