DOI: 10.7860/JCDR/2026/87496.24264

Review Article

Community Section

Nipah Virus Infection: A Narrative Review of Clinical Spectrum, Pathogenesis, and Emerging Preventive and Therapeutic Strategies

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ABSTRACT

Nipah virus (NiV) is known to be an emerging zoonotic pathogen of the Paramyxoviridae family, which was first identified in 1998, and is also associated with high morbidity and mortality due to severe encephalitis and respiratory illness. Transmission occurs through direct contact with infected animals, contaminated food, and human-to-human transmission , thereby further highlighting its epidemic potential. Despite significant advances in understanding its virology, pathogenesis, as well as clinical manifestations, NiV outbreaks continue to pose substantial public health challenges, usually in endemic regions. Current management of NiV remains largely supportive with no licensed antivirals or vaccines available, thus emphasising the need for effective medical countermeasures. Recent therapeutic developments must focus on monoclonal antibodies and antiviral agents, including Remdesivir, which have shown promising efficacy in preclinical studies. Vaccine candidates, including recombinant protein, viral vector, and mRNA-based platforms, are being examined in their early phases of clinical evaluation, showing potential for robust protection of immunity. Future research priorities must include the development of rapid point-of-care diagnosis, strengthening genomic surveillance while also implementing One Health approaches integrating human, animal and environmental data for the prevention of spillover events. Refining animal models and elucidating immune correlates of protection are very important aspects for translating preclinical successes into adequately licensed interventions for management approaches for NiV. Collaborative international frameworks as well as structured R&D roadmaps are critical options for the acceleration of vaccine and therapeutic development, thereby further ensuring rapid deployment during outbreaks. This narrative review article highlights current knowledge on the epidemiology of NiV, pathogenesis, clinical management, as well as emerging preventive-therapeutic strategies while also identifying critical research gaps. It underscores the need for a proactive, integrated approach which combines medical, public health and scientific efforts for the mitigation of the threat of NiV globally.

Keywords: Antibodies, Diagnostics, Epidemiology, Outbreak, Zoonosis

INTRODUCTION

The NiV is a highly pathogenic zoonotic RNA virus which belongs to the Paramyxoviridae family, Henipavirus genus, and is closely related to Hendra virus [1]. It is a recently emergent human pathogen which is capable of causing a wide spectrum of disease in humans and animals, from asymptomatic infection to acute respiratory illness as well as fatal viral encephalitis [1,2]. In humans, NiV infection usually presents with fever, neurological involvement, and severe respiratory symptoms; it is also associated with high case fatality rates, which vary by outbreak as well as surveillance capability [2]. The natural reservoir for NiV is fruit bats of the genus Pteropus; transmission to humans can occur due to having contact with infected animals, contaminated food products (such as date palm sap), or infected persons [2,3]. Due to its high mortality, broad host range, as well as potential for person-to-person transmission, NiV is thereby classified as a Biosafety Level-4 (BSL-4) pathogen, recognised as a priority emerging infectious disease threat by global health authorities [3,4]. Unlike many other paramyxoviruses, NiV exhibits unique virologic properties that help to enable severe human disease, but also many aspects of its transmission as well as pathogenesis remain incompletely understood [4]. There are no licensed vaccines or specific antiviral therapies available, which thereby makes supportive care and preventive public health measures the main aspect of clinical management and outbreak control [4,5].

NiV was first identified during a major outbreak of encephalitis, respiratory disease in pigs and humans in Malaysia-Singapore between 1998 and 1999 [6]. The virus was initially mistaken for another encephalitic pathogen until detailed virologic investigations, including isolation from patients as well as associated animals, showed a previously unknown paramyxovirus, later named after the Malaysian village Sungai Nipah where the first human case was linked [6,7]. The outbreak of NiV was inclusive of hundreds of human cases, and significant mortality also led to the culling of over one million pigs to halt further spread [6]. Following the original emergence in Malaysia, subsequent outbreaks have also occurred almost annually in Bangladesh and the Indian region with distinct epidemiologic patterns [7]. The transmission has been linked more directly with bat-to-human spillover, which usually happens through consumption of fruit or date palm sap contaminated with bat secretions, as well as documented person-to-person spread in several settings [8]. The continued occurrence of all these outbreaks, usually in South Asia, highlights the persistent public health threat posed by NiV as well as the need for enhanced surveillance, research into effective counter measures [8]. This narrative review article further aims to comprehensively summarise current understanding of NiV, including its epidemiology, pathogenesis, clinical management, as well as emerging preventive and therapeutic strategies, while also highlighting critical research gaps.

Global and Indian Epidemiology of NiV Infection

Globally, human infections have been recorded, usually in Bangladesh and India, alongside earlier outbreaks in Malaysia, Singapore and the Philippines [9]. Most epidemiological studies highlight that while the overall number of NiV cases is low as

compared to many other infectious diseases, case-fatality rates are disproportionately high, which further contributes to substantial public health concern where outbreaks occur [9]. Mortality rates in compiled case series are approximately 65% in many outbreaks, thus reflecting severe clinical outcomes as well as limited options for treatment [9,10]. Considering the Indian region, the incidence of NiV has manifested in discrete outbreaks rather than being a continuous endemic transmission, with its first documented event in Siliguri, West Bengal, in the year 2001, inclusive of approximately 66 cases, high case fatality [11]. The second most recognised outbreak of NiV occurred in the Nadia district of West Bengal in 2007 [11]. Beginning in the year 2018, Kerala state further emerged as a recurrent site of NiV spillovers having multiple outbreaks reported throughout 2024 [11,12]. All these events have ranged in size from single isolated cases to clusters of more than 20 confirmed infections in Kozhikode as well as Malappuram districts, along with overall multiple outbreaks occurring over the past two decades [12].

Although proper prevalence data in the general population are limited which is due to the episodic nature of outbreaks, absence of routine serosurveillance as well as targeted surveys in reservoir hosts (inclusive of Pteropus medius fruit bats) across eastern-northeastern India have been conducted for assessment of potential spillover risk [4,13]. NiV infections in humans in India remain geographically focal, usually in Kerala, also previously in West Bengal, rather than widespread, with prevalence confined to outbreak periods as well as their immediate contacts [11,13].

Clinical Features and Symptomatology of NiV Infection

NiV infection presents with a wide spectrum of clinical manifestations, which range from mild, non-specific flu-like symptoms to severe neurological and respiratory disease [14]. The incubation period of NiV usually spans approximately 4 to 14 days after exposure, although longer intervals have been reported in the literature [14,15]. Early clinical features are generally inclusive of fever, headache, myalgia, vomiting, as well as sore throat, which are common but non specific, thereby making early diagnosis challenging in outbreak settings [15,16]. These prodromal symptoms can be accompanied by respiratory complaints such as cough, difficulty breathing, usually in outbreaks due to the NiV-Bangladesh strain [16]. Severe respiratory involvement can further advance to atypical pneumonia, and in some cases, Acute Respiratory Distress Syndrome (ARDS) thus necessitating advanced supportive care [9,16].

The hallmark feature which is related to severe NiV disease is acute encephalitis along with prominent neurological dysfunction [17]. As infection progresses, patients usually show drowsiness, altered consciousness, confusion, and seizures, thereby reflecting the involvement of the central nervous system [17]. Many case series have further documented brainstem dysfunction, myoclonus, as well as other focal neurological signs, which can rapidly deteriorate, resulting in coma within 24-48 hours of severe symptom onset [17,18]. These neurologic features are major determinants of poor outcome, which are seen across multiple outbreaks, usually in South and Southeast Asia [6,18].

Although a small proportion of NiV infections can be asymptomatic, majority of clinically recognised cases result in serious disease along with showing significant morbidity and mortality [19]. Case fatality rates across outbreaks have ranged considerably, but it remains high, thus reflecting the virus's capacity to cause rapid neurological decline as well as severe respiratory compromise [19,20]. Survivors of acute Nipah encephalitis often show long-term neurological sequelae, which are inclusive of seizure disorders and behavioural changes, thereby further highlighting the profound impact of this infection on affected individuals [20]. Clinical Features and Symptomatology of NiV Infection are described in [Table/Fig-1] [6,9,16-20].

Clinical aspect	Description	References
Spectrum of disease	Clinical manifestations range from mild, non specific flu-like illness to severe neurological and respiratory disease	[14]
Incubation period	Typically 4-14 days following exposure; longer incubation periods have been reported	[14,15]
Early (prodromal) symptoms	Fever, headache, myalgia, vomiting, sore throat; symptoms are non specific and complicate early diagnosis during outbreaks	[15,16]
Respiratory manifestations	Cough and difficulty breathing, particularly noted in outbreaks caused by the NiV-Bangladesh strain	[16]
Severe respiratory disease	Progression to atypical pneumonia and, in some cases, Acute Respiratory Distress Syndrome (ARDS), requiring advanced supportive care	[9,16]
Hallmark severe feature	Acute encephalitis with prominent neurological dysfunction	[17]
Neurological manifestations	Drowsiness, altered consciousness, confusion, seizures indicating central nervous system involvement	[17]
Advanced neurological signs	Brainstem dysfunction, myoclonus, and focal neurological deficits; rapid deterioration to coma within 24-48 hours of severe symptom onset	[17,18]
Determinants of poor outcome	Neurological involvement strongly associated with adverse prognosis across South and Southeast Asian outbreaks	[6,18]
Asymptomatic infection	A small proportion of infections may remain asymptomatic	[19]
Disease severity and outcomes	Majority of clinically recognised cases result in severe disease with significant morbidity and mortality	[19]
Case fatality	Fatality rates vary across outbreaks but remain high, reflecting rapid neurological decline and severe respiratory compromise	[19,20]
Long-term sequelae in survivors	Persistent neurological complications including seizure disorders and behavioural changes following acute Nipah encephalitis	[20]

[Table/Fig-1]: Clinical features and symptomatology of Nipah Virus (NiV) infection [6,9,16-20].

Rare and atypical clinical manifestations of NiV infection: Beyond the usual encephalitic and respiratory manifestations of NiV infection, several uncommon clinical features have been documented in case reports and series, thereby further highlighting the capacity of the virus for multisystem involvement [21]. Although it is not universally observed, cardiac involvement like myocarditis, along with associated bradycardia and intractable hypotension, has been described in various outbreaks, thereby suggesting that the virus can affect the cardiovascular system in addition to the central nervous system and lungs [21,22]. In the year 2018 Kerala outbreak, a few patients showed myocarditis, which is a very rare but clinically important manifestation requiring supportive cardiac care beyond conventional management of NiV [22].

Neurological involvement in NiV also extends beyond classic encephalitis, including late-onset or relapsing encephalitis, which can further occur months to years after recovery from the acute phase [17,23]. This phenomenon of delayed neurological deterioration reflects persistent, recrudescent viral activity within the CNS, and it is considered a rare but severe complication which has been documented in longitudinal follow-up studies of survivors [23]. These delayed cases can also present with progressive cognitive decline, behavioural changes, as well as focal neurological deficits, thereby underscoring the need for long-term clinical vigilance in convalescent patients [23].

During acute infection with NiV, few distinctive neurological examination findings have been documented, which further characterise severe involvement of the disease [24]. Brainstem and upper cervical cord dysfunction also noted in NiV include areflexia,

generalised hypotonia, abnormal pupillary responses, impaired oculocephalic (doll's-eye) reflexes, tachycardia, and hypertension [24]. Reduced or absent deep tendon reflexes have been particularly associated with patients having impaired consciousness [24]. Segmental myoclonus, inclusive of focal, rhythmic contractions which most prominently affect the diaphragm but also further involve facial, cervical and limb musculature, has been identified as a notable clinical feature in a few NiV patients [24]. Neuroimaging abnormalities and abnormal chest radiographic findings have been observed in cases of NiV, even in the absence of primary pulmonary pathology, thus indicating its involvement in systemic disease [24].

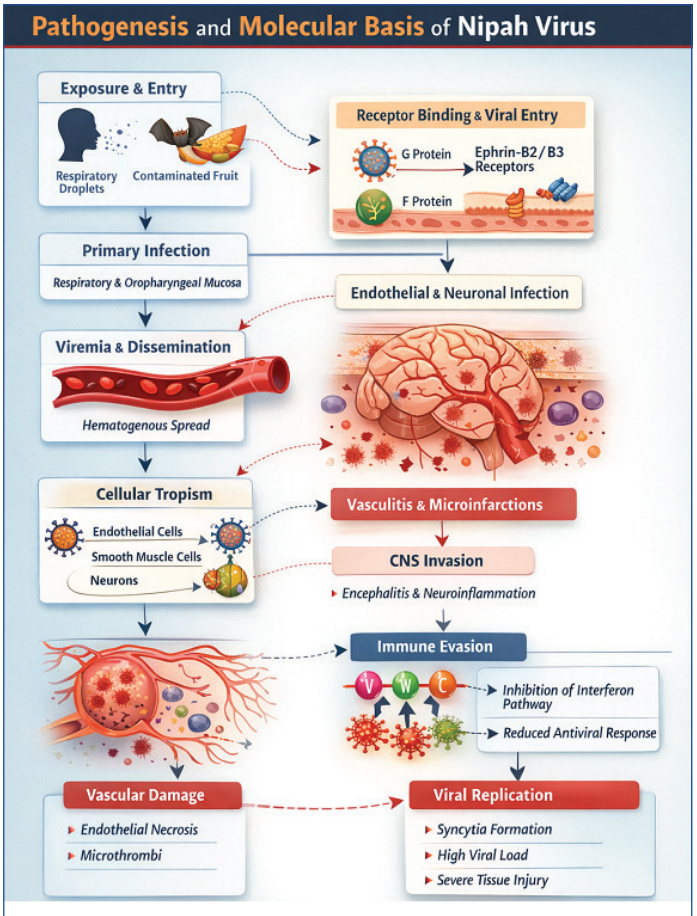
In addition to cardiovascular, delayed CNS complications, unusual haematologic and neuro-ophthalmic signs have been recorded in isolated cases [18]. Some case reports also describe atypical manifestations, which are inclusive of sixth cranial nerve palsy, nystagmus, transient blindness, and sensory deficits, which suggest involvement of specific cranial nerve pathways and localised brainstem dysfunction [18,25]. Other rare clinical observations like nausea, nausea-associated muscle weakness, as well as meningitic features have also been described, although they are infrequent as compared to the core symptoms [25].

Pathogenesis and Molecular Mechanisms of NiV Infection

The pathogenesis of NiV is usually driven by its strong endothelial and neuronal tropism, which further results in the widespread vasculitis, thrombosis, and parenchymal tissue injury [26]. After the entry through respiratory or oropharyngeal mucosa, the virus disseminates haematogenously and further it infects endothelial cells, smooth muscle cells, neurons, along with epithelial cells [26]. A defining pathological feature of NiV infection is known to be the systemic vasculopathy, which is characterised by endothelial syncytia formation, vascular necrosis, and microinfarctions usually within the CNS [27]. This vascular damage facilitates viral entry into the brain, which leads to encephalitis as well as contributes to severe neurological manifestations observed in some of the fatal cases [20,28]. Histopathological studies mostly show fibrinoid necrosis of small vessels, perivascular inflammation, and neuronal infection, thereby underscoring the pivotal role of endothelial dysfunction in the progression of NiV [29].

At the molecular level, NiV is known to be an enveloped, negative-sense, single-stranded RNA virus whose pathogenicity is mostly mediated by its surface glycoproteins G and F [30]. The attachment (G) glycoprotein binds with high affinity to host cell receptors ephrin-B2 and ephrin-B3, which are usually expressed on endothelial cells and neurons, thereby explaining the neurovascular predilection of the virus [30]. Following receptor binding, the Fusion (F) protein further helps to facilitate viral-host membrane fusion, thus enabling entry of the viral genome into the host cytoplasm [30]. Intracellular replication occurs in the cytoplasm, and it is associated with extensive cell-cell fusion, which results in multinucleated syncytia that promote direct viral spread while evading extracellular immune surveillance [30,31].

NiV further enhances its virulence through potent immune evasion mechanisms, which are mediated by non-structural proteins encoded by the P gene, usually the V, W, and C proteins [30,31]. All of these proteins inhibit host innate immune responses through antagonising type I interferon signalling pathways, including suppression of STAT1 and STAT2 phosphorylation and nuclear translocation [32]. This impairment of antiviral signalling thereby allows unchecked viral replication and dissemination, thus contributing to high viral loads as well as severe tissue damage [32]. The combination of efficient receptor-mediated entry, endothelial disruption, neuronal invasion, and immune suppression forms the molecular basis of the high pathogenicity of NiV [30-32]. The pathogenesis and molecular basis of NiV is depicted in [Table/Fig-2].



[Table/Fig-2]: The pathogenesis and molecular basis of Nipah Virus (NiV); Author-created image with AI assistance. NiV: Nipah virus; G: Attachment glycoprotein; F: Fusion glycoprotein; STAT: Signal Transducer and Activator of Transcription; IFN: Interferon; CNS: Central Nervous System.

Organ-wise Pathology of Acute NiV Infection

Autopsy-based studies of fatal human cases showed that acute NiV infection is a multisystem disease having prominent respiratory and neurovascular involvement [24]. Gross findings are mostly non specific, though small necrotic foci can usually be identified [24]. The respiratory tract further represents an important early site of pathology where viral antigen can be detected in bronchiolar as well as lower respiratory epithelial cells, along with shedding occurring via nasopharyngeal and tracheal secretions during early illness [24,33]. Histologically, pulmonary lesions include necrotising alveolitis with associated haemorrhage, pulmonary oedema and features resembling aspiration pneumonia. Multinucleated giant cells can be present within alveolar septa and airspaces, which are accompanied by intra-alveolar inflammatory infiltrates [33]. In severe cases of NiV, inflammatory mediator release from infected lower airway epithelium can further contribute to an ARDS-like presentation of patients [33]. Despite involvement of the lower airway, significant structural alterations in the tracheal and bronchial epithelium are relatively uncommon in patients [33].

Systemic dissemination of NiV further results in widespread vascular-centred injury across multiple organs, including the brain, lungs, kidneys and heart, while large cerebral arteries are usually spared [24]. Histopathologically, medium- to small-calibre vessels show endothelial ulceration, mural inflammatory cell infiltration, fibrinoid necrosis and luminal thrombosis [24]. Immunohistochemical and ultrastructural studies further showed viral antigen, nucleocapsid particles within affected vascular tissues, thus confirming direct involvement of the microvasculature in NiV cases [24,33]. Renal pathology usually includes glomerular capillary microthrombi, inflammatory cell infiltration and occasional multinucleated cells along the glomerular periphery, suggestive of podocyte injury [24]. Cardiac tissue can also show vascular-centred lesions, lymphoid organs, which are inclusive of the spleen and lymph nodes,

occasionally demonstrating multinucleated cells with detectable viral antigen, thus reflecting systemic spread [24].

The central nervous system remains the most extensively affected organ system [24]. Microscopically, widespread vascular-associated lesions are observed in both grey and white matter, which are often accompanied by necrotic plaques adjacent to compromised vessels [24]. These lesions are associated with thrombosis, parenchymal oedema and inflammatory infiltrates composed of neutrophils, macrophages, lymphocytes, and reactive microglia [24]. Neurons within affected regions can contain eosinophilic cytoplasmic inclusions as well as less frequently intranuclear inclusions along with peripheral chromatin margination, thereby consistent with paramyxoviral morphology [24,33]. Viral antigen has been demonstrated within neurons, neuronal processes and occasionally ependymal and glial cells [24,33]. Entry into CNS is proposed to occur via haematogenous spread through cerebral vasculature, choroid plexus or through an anterograde olfactory neuronal route [33]. Collectively, all these findings highlight organ-specific yet interconnected pathological processes that underlie severe acute NiV infection [24,33]. Organ-wise pathology of acute NiV infection is depicted through [Table/Fig-3] [24,33].

Organ/System	Histopathological features	Additional remarks	References
Respiratory system (lungs and airways)	Necrotising alveolitis, haemorrhage, pulmonary oedema, aspiration pneumonia-like features; multinucleated giant cells in alveolar septa and airspaces; intra-alveolar inflammatory infiltrates	Early site of infection; viral antigen in bronchiolar and lower respiratory epithelium; viral shedding via nasopharyngeal/ tracheal secretions; ARDS-like presentation; minimal structural changes in trachea/ bronchi	[24,33]
Vascular system (systemic microvasculature)	Endothelial ulceration, mural inflammatory infiltrate, fibrinoid necrosis, luminal thrombosis in small to medium vessels	Direct viral involvement confirmed by viral antigen and nucleocapsid particles; large cerebral arteries typically spared	[24,33]
Central nervous system (brain)	Widespread vascular-associated lesions in gray and white matter; necrotic plaques near vessels; thrombosis, oedema, mixed inflammatory infiltrate (neutrophils, macrophages, lymphocytes, microglia); neuronal eosinophilic cytoplasmic inclusions and occasional intranuclear inclusions	Most extensively affected organ; viral antigen in neurons, glial and ependymal cells; CNS entry via haematogenous, choroid plexus, or olfactory route	[24,33]
Kidneys	Glomerular capillary microthrombi, inflammatory infiltration; occasional multinucleated cells at glomerular periphery (suggestive of podocyte injury)	Reflects systemic vascular involvement	[24]
Heart	Vascular-centered lesions	Part of systemic dissemination	[24]
Lymphoid organs (Spleen, Lymph Nodes)	Occasional multinucleated cells with detectable viral antigen	Indicates systemic spread of infection	[24]

[Table/Fig-3]: Organ-wise pathology of acute Nipah Virus (NiV) infection [24,33].

Genetic and phylogenetic classification of NiV: Phylogenetic and genomic studies have identified two major genetic lineages or clades, which correlate with geographic origin as well as disease characteristics [34]. The Malaysian clade (NiV-M) is inclusive of isolates from original outbreaks in Malaysia and Singapore, while the Bangladesh/India clade (NiV-B) includes strains which are responsible for outbreaks in Bangladesh and India [34]. All these clades show consistent nucleotide as well as amino acid differences across structural, non structural genes, and NiV-B strains have been associated to higher human-to-human transmissibility along with greater pathogenicity in some models [35,36]. Sublineages within such clades also exist, usually within the Bangladesh lineage, thereby further highlighting ongoing genetic diversity, which has implications for virulence, transmission dynamics, and public health responses [35,36].

NiV is a member of the genus Henipavirus within the Paramyxoviridae, which possesses a single-stranded, non segmented, negative-sense RNA genome organised in the order 3′-N-P-M-F-G-L-5′ [37]. The viral envelope contains two surface glycoproteins, which are important for its infectivity: attachment glycoprotein (G), which mediates host cell receptor binding and fusion glycoprotein (F), which facilitates membrane fusion and viral entry [37,38]. NiV utilises ephrin-B2 and ephrin-B3 receptors, which are abundantly expressed on endothelial, epithelial, and neuronal tissue, thus explaining the virus's pronounced neurotropism as well as systemic vasculitis observed in severe disease [37,38].

At the molecular level, conformational changes in G protein following receptor engagement trigger activation of the F protein, resulting in fusion of the viral and host cell membranes along with formation of multinucleated syncytia [38]. Specific amino acid residues within the receptor-binding domain of G protein have been shown to play a role in the regulation of binding affinity as well as fusion efficiency [38]. Glycosylation sites on F protein cause modulation of fusion kinetics, which can contribute to immune evasion by shielding neutralising epitopes [38]. The matrix (M) protein orchestrates viral assembly and budding at the plasma membrane, whereas phosphoprotein (P) gene products, inclusive of V and W accessory proteins, play a central role in antagonising host interferon-mediated antiviral responses, thereby enhancing viral pathogenicity [37,38]. These coordinated molecular interactions provide multiple therapeutics as well as vaccine targets [38].

Diagnosis of Nipah Virus (NiV) Infection

The diagnosis of NiV infection depends mainly upon a combination of clinical suspicion, epidemiological aspects and laboratory confirmation of viral pathogen [39]. Clinically, NiV infection usually presents along with acute febrile illness, which is accompanied by headache, myalgia, vomiting, as well as sore throat, which can rapidly progress into encephalitis, severe respiratory disease [39,40]. Due to non specific early symptoms, a high index of suspicion is said to be very essential in patients from endemic regions or those who have a history of exposure to bats, infected animals, as well as confirmed human cases [40]. Neuroimaging, which mainly includes Magnetic Resonance Imaging (MRI), mostly shows multiple small, discrete hyperintense lesions in subcortical as well as deep white matter on T2-weighted, Fluid-Attenuated Inversion Recovery (FLAIR) sequences, which are although not pathognomonic, but can further support clinical diagnosis when correlated with epidemiological risk factors [29,41].

Laboratory confirmation remains the main aspect of NiV diagnosis. Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) is known to be the most widely used as well as sensitive method for detection of viral RNA during the acute phase of illness [42]. RT-PCR can be performed on various clinical specimens, including throat-nasal swabs, Cerebrospinal Fluid (CSF), blood, urine, and endotracheal aspirates, along with respiratory samples often yielding higher viral loads in patients having involvement of the pulmonary system [42,43]. Viral isolation in cell culture thereby

provides definitive evidence of infection, but it is only restricted to Biosafety Level 4 (BSL-4) laboratories because of the high pathogenicity of the virus, limiting its routine diagnostic utility [43,44].

Serological assays also play an important complementary role usually in later stages of illness, and also for retrospective diagnosis. Enzyme-Linked Immunosorbent Assays (ELISA) have been used for the detection of NiV-specific IgM and IgG antibodies [43,45]. IgM indicates recent infection, while IgG suggests past exposure or recovery phase [45]. Neutralisation tests are considered the gold standard for serological confirmation, but like viral culture it also require high-containment facilities [46]. Together, molecular-serological methods, which are interpreted in appropriate clinical as well as epidemiological context, further form a robust diagnostic framework for NiV infection [46]. Diagnostic modalities for NiV infection are elaborated in [Table/Fig-4] [29,39-46].

Differential Diagnosis of Nipah Virus (NiV) Infection

The differential diagnosis of NiV is broad, usually in endemic regions where acute febrile encephalopathy as well as severe respiratory illness are common clinical presentations. Among viral causes, Japanese encephalitis, Herpes simplex encephalitis, and West Nile virus infection are important considerations [4,47]. All of these conditions usually present with fever, altered sensorium, seizures and focal neurological deficits thereby closely mimicking NiV-associated encephalitis [47]. However, NiV is more frequently associated with rapidly progressive disease, higher case fatality rates along with concurrent respiratory involvement which is less prominent in most arboviral encephalitides [3,48]. Neuroimaging in NiV patients can show multiple small, discrete lesions in subcortical and deep white matter whereas herpes simplex encephalitis classically involves temporal lobes thus aiding into its differentiation [49].

In addition to viral aetiologies, bacterial and other infectious causes which are inclusive of acute bacterial meningitis, scrub typhus and leptospirosis must also be considered, usually in tropical settings [50-52]. These infections can present having fever, headache, altered mental status and multi-organ involvement thus overlapping significantly with NiV infection [50-52]. Bacterial meningitis usually shows neutrophilic pleocytosis, marked hypoglycorrhachia in CSF while scrub typhus can show eschar also it responds well to doxycycline thus distinguishing it clinically [50,51]. Leptospirosis can present with jaundice and renal dysfunction features which are not typically dominant in NiV patients [52].

Respiratory-dominant presentations of NiV can resemble severe viral pneumonias such as Coronavirus Disease 2019 (COVID-19) and influenza; both of which can result in ARDS [53]. All these infections share symptoms such as fever, cough and hypoxia, but NiV is more likely to have simultaneous or subsequent neurological deterioration [9,53]. Epidemiological context such as exposure to bats, pigs or outbreak clusters, along with laboratory confirmation via RT-PCR or serology, remains an important aspect in the definitive diagnosis of NiV [9,29]. Thus, distinguishing NiV from its differentials relies on a combination of clinical pattern recognition, imaging findings, laboratory parameters, and exposure history [29]. Differential diagnosis of NiV infection is mentioned in [Table/Fig-5] [4,9,47,49-53].

Emerging diagnostic technologies for NiV infection: The emerging diagnosis of NiV has focused on the development of rapid, field-deployable platforms for enabling early case detection during outbreaks of NiV. Isothermal nucleic acid amplification techniques like Loop-mediated Isothermal Amplification (LAMP) as well as Recombinase Polymerase Amplification (RPA) have emerged further as promising alternatives for the conventional molecular assays [29,54]. These methods thereby allow amplification of NiV genetic material at a constant temperature, reducing assay time and dependence on sophisticated laboratory infrastructure [54].

Diagnostic modality	Specimen / method	Key findings/ utility	Limitations	Reference No.
Clinical and epidemiological assessment	Clinical evaluation with exposure history	Acute febrile illness with headache, myalgia, vomiting, sore throat; rapid progression to encephalitis or severe respiratory disease; high suspicion required in endemic areas or exposure to bats, infected animals, or human cases	Early symptoms are non specific	[39,40]
Neuroimaging (MRI)	MRI brain (T2-weighted, FLAIR sequences)	Multiple small, discrete hyperintense lesions in subcortical and deep white matter supporting diagnosis when correlated with epidemiological risk	Not pathognomonic	[29,41]
Real-Time RT-PCR	Throat/nasal swabs, CSF, blood, urine, endotracheal aspirates, respiratory samples	Most sensitive and widely used method for detecting viral RNA during acute phase; higher viral load in respiratory samples in pulmonary involvement	Limited to acute phase	[42,43]
Viral isolation (cell culture)	Clinical specimens cultured in specialised labs	Provides definitive evidence of NiV infection	Restricted to BSL-4 laboratories; not suitable for routine diagnosis	[43,44]
ELISA (Serology)	Serum samples	Detection of NiV-specific IgM (recent infection) and IgG (past exposure/ recovery); useful in later stages and retrospective diagnosis	Not useful in early acute phase	[43,45]
Neutralisation tests	Serum samples	Gold standard for serological confirmation	Requires high-containment (BSL-4) facilities	[46]

[Table/Fig-4]: Diagnostic modalities for Nipah Virus (NiV) infection [29,39-46].
NiV: Nipah virus; MRI: Magnetic Resonance Imaging; T2: T2-weighted magnetic resonance sequence; FLAIR: Fluid-Attenuated Inversion Recovery; RT-PCR: Reverse Transcription Polymerase Chain Reaction; CSF: Cerebrospinal Fluid; ELISA: Enzyme-Linked Immunosorbent Assay; IgM: Immunoglobulin M; IgG: Immunoglobulin G; BSL-4: Biosafety Level 4

Differential diagnosis	Similarity with NiV infection	Differentiating features	References
Japanese encephalitis	Acute febrile encephalopathy, seizures, altered sensorium	Typically lacks severe respiratory involvement; MRI often shows thalamic involvement	[4,47]
Herpes simplex encephalitis	Fever, altered mental status, focal neurological deficits	Predominant temporal lobe involvement on MRI; PCR positive for HSV in CSF	[47,49]
West Nile virus infection	Fever, encephalitis, neurological deficits	More common flaccid paralysis; usually milder respiratory symptoms	[47]

Acute bacterial meningitis	Fever, headache, altered sensorium	CSF shows neutrophilic pleocytosis, low glucose, high protein; responds to antibiotics	[51]
Scrub typhus	Fever, encephalopathy, multi-organ involvement	Presence of eschar; rapid response to doxycycline	[50]
Leptospirosis	Fever, headache, systemic involvement	Jaundice, renal failure (Weil's disease); serology positive for Leptospira	[52]
COVID-19	Fever, cough, hypoxia, ARDS	Predominantly respiratory; neurological involvement less severe and less frequent	[9,53]
influenza	Fever, respiratory symptoms, ARDS in severe cases	Usually self-limiting; lacks severe encephalitis and high fatality seen in NiV	[9,53]

[Table/Fig-5]: Differential diagnosis of Nipah Virus (NiV) infection[4,9,47,49-53].
NiV: Nipah virus; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; HSV: Herpes simplex virus; CSF: Cerebrospinal fluid; ARDS: Acute respiratory distress syndrome

NiV-specific RT-LAMP assays can help to achieve high analytical sensitivity and specificity thus making them a particularly suitable option for resource-limited settings, point-of-care screening during outbreak scenarios [54].

The development of lateral flow immunoassays and microfluidic chips, which are capable of detecting NiV antigens or host immune signatures within minutes, can prove helpful in cases of NiV [55,56]. Multiplex bead-based assays, syndromic panels have been designed for simultaneously detecting NiV alongside other viral encephalitides as well as acute febrile illnesses, thereby improving differential diagnosis in endemic regions of NiV [55]. All these approaches not only shorten turnaround time but also help further to reduce diagnostic ambiguity in early disease stages when clinical features overlap with other viral infections [55].

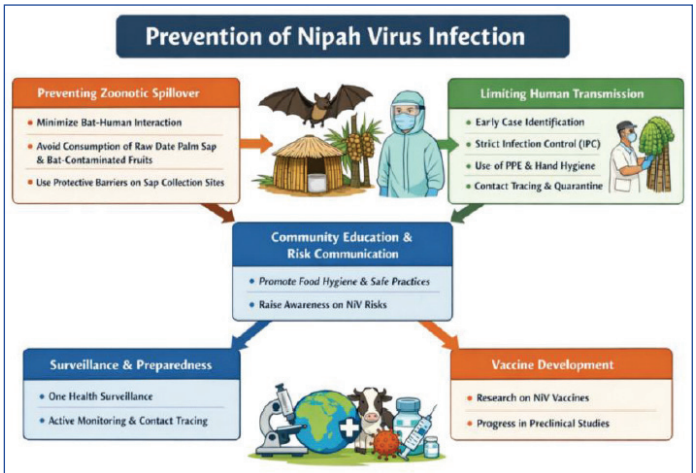
In addition, host-response and genomic-based strategies are also gaining attention as useful adjunctive diagnostic tools [57]. Transcriptomic and proteomic profiling studies have further identified distinct host biomarker signatures, which are inclusive of interferon-stimulated genes as well as inflammatory mediators, which can help discriminate NiV infection from other causes of encephalitis [57,58]. Advancements in Next-Generation Sequencing (NGS) have helped further enabled unbiased metagenomic detection of NiV directly from clinical samples, thus facilitating early identification of novel strains and real-time molecular epidemiology related to NiV [58].

Prevention of NiV Infection

Prevention of NiV is mainly dependent upon interrupting zoonotic spillover and limiting human-to-human transmission [59]. As fruit bats of the genus Pteropus are known to be the natural reservoir, minimising bat-human interaction is a central aspect of prevention strategies [59,60]. Public health measures which are inclusive of avoiding consumption of raw date palm sap, fruits partially eaten by bats as well as unwashed or fallen fruits in endemic regions [60]. Simple physical barriers like bamboo skirts, protective coverings over date palm sap collection sites have been shown to reduce contamination by secretions of bat thereby lowering risk of spillover events [61]. Community education, risk communication campaigns which focus on food hygiene as well as safe agricultural practices remain crucial components of primary prevention [61].

Human-to-human transmission, usually in healthcare as well as household settings, requires strict Infection Prevention and Control (IPC) measures [62]. The early case identification, patient isolation, adherence to standard, contact, droplet precautions, along with airborne precautions, is recommended during aerosol-generating procedures [62]. Use of Personal Protective Equipment (PPE), hand hygiene, environmental disinfection, and safe handling of biological specimens are essential for the prevention of nosocomial outbreaks [62,63]. Contact tracing, quarantine of high-risk contacts, and active surveillance have been consistently helping in the limitation of secondary transmission during outbreaks, mainly in densely populated settings [63].

At the population level, surveillance and preparedness play an important role in the prevention of the spread of NiV [63]. Strengthening the concept of One Health-based surveillance systems, which integrates human, animal, and environmental health data, further allows early detection of NiV circulation as well as spillover risk [64]. Ongoing research efforts also highlight progress in NiV vaccine development, which is inclusive of recombinant viral vector and subunit vaccine candidates that have shown promising immunogenicity as well as protective efficacy in preclinical models [29,65]. Although no licensed human vaccine is currently available, these advances, when further combined with sustained surveillance, outbreak preparedness, and community-level interventions, form the main aspect of NiV prevention strategies [29]. Prevention strategies for NiV infection are depicted in [Table/Fig-6].



[Table/Fig-6]: Prevention strategies for Nipah Virus (NiV) infection. Author-created image with AI assistance. NiV: Nipah virus; IPC: Infection Prevention and Control; PPE: Personal Protective Equipment.

Current progress in NiV vaccine platforms: Subunit vaccines, which are based upon recombinant NiV surface glycoproteins (especially attachment G and fusion F proteins), have shown strong immunogenicity in animal models such as mice and pigs, inducing both neutralising antibodies as well as cellular responses which correlate with protection against infection in challenge studies [66,67]. These protein-based constructs, usually in multimeric and adjuvanted forms, show enhanced antigenicity, which is considered promising candidates for further development because they focus the immune system on key viral antigens proven to elicit neutralising activity [68].

Beyond having such traditional subunit vaccines, several vectored as well as mRNA platforms originally developed during the COVID-19 pandemic are being repurposed for NiV [68]. An mRNA vaccine that encodes soluble G glycoprotein has elicited potent neutralising antibody responses against multiple NiV strains, but it is observed in preclinical models which is further advancing through early clinical evaluation for assessment of safety, immune responses in humans [61,69]. Adenoviral vectored vaccines, which include ChAdOx1 NipahB, have received regulatory support under accelerated pathways (e.g., EMA PRIME designation) that are now undergoing Phase II trials in regions where the virus is endemic to better define immunogenicity, safety, as well as potential protective efficacy [70,71]. These new emerging platforms that are combined with insights from animal model studies, immunoinformatics-driven multi-epitope designs reflect a broad evolving pipeline which is aimed at overcoming historical challenges in NiV vaccine development, including the sporadic nature of outbreaks along with the need for robust correlates of protection [68].

Building upon advances in molecular understanding of the entry of NiV as well as immune evasion mechanisms, several vaccine strategies are specifically designed for targeting structurally conserved neutralising epitopes within G receptor-binding domain and prefusion-stabilised F protein [38,72]. Structural biology studies have enabled rational antigen design for improvement of epitope exposure as well as enhanced neutralising antibody generation [72]. Stabilisation of prefusion F conformations, which is very similar to strategies employed in other paramyxoviruses, has been shown to significantly improve immunogenicity in preclinical systems [38,72].

In addition to humoral immunity, emerging vaccine platforms also aim to induce robust cellular immune responses, usually inclusive of CD8+ T-cell-mediated cytotoxicity, which can help with viral clearance in systemic, neuroinvasive disease [38]. Advances into immuno-informatics as well as multi-epitope design approaches are being explored for optimisation of antigen presentation along with broadening of strain coverage across all the circulating variants [38]. Despite having a promising preclinical efficacy, translation directly into human usage remains a very challenging aspect due to sporadic outbreak patterns and difficulty in conducting large-scale efficacy trials, thereby highlighting the need for adaptive regulatory frameworks and outbreak-responsive vaccination strategies [38,72].

Current Treatment and Supportive Management of NiV Infection

Current clinical management of NiV is usually supportive, as there are no licensed antiviral therapies or adequately reliable vaccines available to date [73]. Patients must be isolated promptly by taking strict infection-control measures to prevent nosocomial-community transmission, as well as supportive care focuses on maintaining airway, breathing, and circulation while also managing fluid electrolyte balance and providing mechanical ventilation for respiratory failure or severe encephalitis when needed [73]. Symptomatic treatment also includes seizure control, critical care interventions in an ICU setting for patients having neurological-respiratory complications, which are common manifestations of severe NiV [73,74]. Isolation and rigorous barrier nursing practices are essential because human-to-human transmission through body fluids can occur, and rapid diagnostic confirmation (e.g., RT-PCR) helps to further guide management while it also helps to determine when patients can be safely discharged from isolation after negative tests and clinical recovery [3,75].

Although no specific antiviral drugs are officially approved, several therapeutic agents have been used on a compassionate, investigational basis as well as evaluated in preclinical or limited clinical contexts [76]. Ribavirin has historically been administered during outbreaks, with inconsistent effects on mortality, and its efficacy remains uncertain despite recommendations for use when no alternatives exist [76,77]. Experimental antivirals such as remdesivir and favipiravir have shown protective effects in animal models, and human monoclonal antibodies such as m102.4, which are among the most promising candidates under investigation, have shown neutralising potential against NiV in non human primate studies [78,79]. However, routine clinical usage of these agents is not established, and there is an ongoing need for well designed clinical trials for determining their safety and effectiveness [78]. Current treatment and management strategies for Nipah Virus (NiV) infection are described in [Table/Fig-7] [3,73,75-79].

Emerging therapeutic and preventive modalities in NiV: Recent advances in NiV therapeutics are usually focused on next-generation immunotherapies usually monoclonal Antibodies (mAbs) that neutralise the virus [79]. Experimental mAbs like hu1F5 have shown superior efficacy in non human primate models as compared to the earlier candidates such as m102.4, with complete protection observed even at reduced doses when administered post-exposure,

Aspect	Management strategy	Key details	Reference No.
Overall treatment approach	Supportive care	No licensed antiviral therapies or reliable vaccines available; management is primarily supportive	[73]
Infection control	Patient isolation and strict IPC measures	Prevents nosocomial and community transmission; barrier nursing essential due to body fluid–mediated spread	[3,73,75]
Airway and respiratory support	Airway protection and mechanical ventilation	Required for respiratory failure or severe encephalitis	[73]
Haemodynamic management	Fluid and electrolyte balance	Maintenance of circulation and prevention of shock	[73]
Neurological management	Seizure control and ICU care	Addresses encephalitis and neurological complications in severe cases	[73,74]
Diagnostic support	RT-PCR confirmation	Guides clinical management and determines safe discontinuation of isolation	[3,75]
Investigational antivirals	Ribavirin	Used during outbreaks with inconsistent mortality benefit; efficacy remains uncertain	[76,77]
Experimental antivirals	Remdesivir, favipiravir	Demonstrated protective effects in animal models	[78]
Immunotherapy	Monoclonal antibody (m102.4)	Shows neutralising potential in non human primate studies	[78,79]
Evidence limitations	Need for clinical trials	Routine clinical use not established; safety and efficacy require validation	[78]

[Table/Fig-7]: Current treatment and management strategies for Nipah Virus (NiV) infection [3,73,75-79].
NiV: Nipah virus; IPC: Infection prevention and control; ICU: Intensive care unit; RT-PCR: Reverse transcription polymerase chain reaction

thereby further supporting their potential for both therapeutic usage and post-exposure prophylaxis in humans [79,80]. Additionally, systematic evaluations of potential treatments indicate that combining neutralising mAbs along with antiviral agents, including remdesivir, could be a promising strategy for enhancement of early treatment efficacy, with these candidates now prioritised for clinical trial assessment [79,81]. Such therapeutic development aims not only to improve survival, but it also helps to provide tailored intervention options which can be deployed rapidly in outbreak settings, usually for high-risk contacts and healthcare workers [81].

Several vaccine candidates, which are inclusive of recombinant protein, viral vector, and mRNA-based approaches, have entered into their early-phase clinical evaluation, with Phase I trials assessing appropriate safety, tolerability as well as immunogenicity in healthy volunteers [66,67]. All of these emerging vaccine platforms are adequately designed for eliciting robust immune responses against important viral glycoproteins, thus potentially offering pre-exposure protection which could be critical in endemic regions or for populations at high risk of exposure [66,67]. Continued clinical research and trial outcomes will prove as an essential factor for advancing these candidates toward licensure as well as public health usage, thus representing a paradigm shift from reactive management toward a proactive prevention of NiV [65,68].

Future Directions and Research Priorities for NiV Infection

Future research on NiV is increasingly guided by a need to close critical knowledge gaps regarding its diagnosis, genomic

surveillance, as well as One Health approaches [82]. Despite having advances in understanding of viral entry mechanisms and early vaccine development, existing literature further emphasises persistent shortcomings in point-of-care diagnostic tools which can rapidly detect infection during outbreaks while also integrating animal-human surveillance data for prevention of spillover events [82]. Strengthening of genomic surveillance approaches, integrating interdisciplinary data from wildlife reservoirs, livestock, and human populations are important for anticipating as well as mitigating future spillovers of NiV [38,82]. A priority for upcoming research must be focused on refining high-throughput sequencing and field-adaptable assays which can further operate in resource-limited settings where outbreaks of NiV usually recur [38].

There is an unmet need to advance promising candidates, including live-attenuated, subunit, viral vector, and mRNA-based vaccines, through later-phase clinical trials to conclusively determine safety, immunogenicity, as well as real-world effectiveness [83]. Enhanced understanding regarding protective immune correlates, continued development of robust animal models will support this translational pipeline, thereby helping to bridge the gap between experimental successes and licensed products [83]. Moreover, international co-operative frameworks, structured R&D roadmaps further prioritise medical counter measures includes from basic research through advanced development and deployment, are being promoted further for acceleration of global readiness against future NiV outbreaks [83,84].

CONCLUSION(S)

NiV remains a highly pathogenic emerging zoonotic threat, having significant morbidity and mortality because of its neurotropic and respiratory involvement. Despite having advances in understanding its virology, transmission, pathogenesis, and diagnostic limitations, the absence of licensed antivirals and sporadic outbreaks pose ongoing challenges. Supportive care, strict infection control, and public health measures remain important aspects for the management of NiV. Emerging vaccine platforms, monoclonal antibodies, and point-of-care diagnosis offer promise, while integrated One Health surveillance, genomic monitoring, and translational research are very crucial for effective prevention, outbreak preparedness, along with global containment of NiV.

Authors' contribution: PJ: Contributed to the conceptualisation, literature review, data collection, and drafting of the manuscript; SC: Provided supervision, critically revised the manuscript for important intellectual content, and approved the final version; BS: Contributed to literature review, data interpretation, manuscript drafting, and formatting of tables and figures. All authors read and approved the final manuscript.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 22, 2026
- Manual Googling: Jun 13, 2026
- iThenticate Software: Jun 15, 2026 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 18, 2026**
Date of Peer Review: **Feb 28, 2026**
Date of Acceptance: **Jun 17, 2026**
Date of Publishing: **Sep 01, 2026**