Review

Nipah Virus Infection: Diagnostic, Clinical, and Preventive Considerations for Clinicians

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Abstract

Nipah Virus (NiV) is a highly virulent zoonotic henipavirus responsible for recurrent outbreaks across South and Southeast Asia and remains a priority global health threat. Fruit bats of the genus Pteropus serve as the natural reservoir, with transmission to humans occurring through contaminated food products, infected intermediate hosts, or person-to-person spread. Clinical illness ranges from nonspecific febrile disease to rapidly progressive encephalitis and severe respiratory failure, with reported case fatality rates often exceeding 40 percent. This narrative synthesis reviews the evolving epidemiology, phylogenetic diversity, transmission pathways, clinical spectrum, diagnostic approaches, and current management strategies of NiV infection. Persistent seasonal spillovers, limited therapeutic options, the absence of licensed human vaccines, and challenges in early detection continue to hinder containment efforts. Strengthening One Health surveillance, expanding laboratory capacity, and accelerating vaccine and antiviral development remain critical priorities to mitigate future outbreaks and reduce associated morbidity and mortality.

Keywords: NiV; zoonotic spillover; henipavirus; acute encephalitis; one health surveillance

Introduction

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Nipah Virus (NiV) is a highly virulent zoonotic paramyxovirus of the genus *Henipavirus* and family *Paramyxoviridae* [1]. NiV was first identified in an outbreak among pig farmers in Malaysia in 1998. Since then, it has been observed in many other nations such as Singapore, Bangladesh, India, and the Philippines [2,3]. The virus is naturally maintained in fruit bats of the genus *Pteropus*, which act as reservoir hosts and facilitate periodic transmission into domestic animals and human populations [4,5]**.** Human infection may occur through direct contact with infected animals, ingestion of tainted food items like raw date palm sap, or human-to-human transmission in healthcare and community settings [6,7]. The clinical spectrum of a NiV infection in humans is broad, ranging from mild feverish illness to severe acute encephalitis and respiratory disease, with substantial fatality rates [2,8,9]. The mortality rate of NiV infections has ranged from approximately 40% to 100% across reported outbreaks [10]. Although sustained human-to-human infection is confined to South and South-east Asia only, due to the combination of exceptionally high mortality rate, limited therapeutic options, lack of approved vaccination, and the potential for nosocomial and community spread, the World Health Organization (WHO) has listed the NiV as a priority pathogen requiring urgent research and development attention [11]. Furthermore, NiV has been internationally categorized as a Biosafety Level-4 agent, reflecting its extreme virulence and lack of effective countermeasures [12].

Despite its currently restricted geographic distribution, the NiV poses a disproportionate public health challenge due to its epidemic potential, respiratory transmission, and the absence of specific antiviral therapy or approved vaccines [13,14]. The unpredictable nature of spillover events, combined with environmental changes, agricultural intensification, and increasing human encroachment into bat habitats, creates favorable conditions for future outbreaks [15]. Furthermore, limited diagnostic capacity in rural settings, delayed recognition of index cases, and fear-driven social responses complicate containment efforts. In the current global context, where emerging infections are being actively examined for the possibility of becoming pandemics, the NiV remains a priority pathogen for research and preparedness. Its recurring reappearance highlights persistent gaps in surveillance, risk communication, and cross-sectoral collaboration within the One Health framework. Therefore, understanding the evolving epidemiology and public health implications of the NiV is essential for strengthening outbreak preparedness and mitigating the impact of future spillover events.

By synthesizing the current body of evidence and identifying critical knowledge gaps, this review aims to inform clinicians, researchers, and public health stakeholders and to support the development of more effective surveillance, diagnostic, and prevention strategies for NiV infection in endemic and emerging settings. A comprehensive literature search was conducted across multiple databases, including Web of Science, Scopus, PubMed, SciELO, LILACS, Latindex, and ScienceDirect. Additional support was obtained through evidence assessment using the OpenEvidence and VeraHealth platforms; however, this work does not constitute a formal systematic or scoping review. The search strategy was designed to ensure both breadth and specificity in accordance with the objectives of this narrative review. Keywords included “Nipah Virus (NiV)”, “epidemiology of NiV”, “transmission dynamics”, “clinical manifestations of NiV”, “diagnosis of NiV”, “treatment and supportive care”, and “prevention and control strategies”. Eligible studies were those presenting original data or relevant clinical and epidemiological insights. Articles were excluded if they contained incomplete or overlapping datasets or lacked access to full text. These criteria were applied to maintain methodological rigor and ensure the validity and relevance of the synthesized evidence.

Phylogenetic diversity

The single-stranded, negative-sense RNA molecule that comprises the NiV genome is approximately 18.2 kilobases (kb) long [16]. The virus has a non-segmented genome and is pleomorphic and enveloped [17]. Nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), glycoprotein (G), and large polymerase (L) are the six structural proteins that make up the viral genome. The virus may infect a wide variety of mammalian hosts thanks to these proteins, which are

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crucial for viral replication, host immune evasion, and transmission. Fruit bats (Pteropus species) are the virus's natural reservoir [18,19]. Phylogenetic analysis classifies NiV into two major lineages: the Malaysia-lineage (NiV-MY), identified in Malaysia and Cambodia, and the Bangladesh-lineage (NiV-BD), reported in Bangladesh and India [20]. The two NiV lineages exhibit are nearly identical in genome length, differing primarily by an additional six nucleotides in the 5′ non-translated region of the F gene in the Bangladeshi strain. Although the overall nucleotide sequence similarity between lineages is approximately 91.8%, infections caused by the Bangladeshi lineage have been associated with higher mortality. Moreover, NiV isolates from India show close genetic similarity to the Bangladeshi lineage, demonstrating 99% and 97% sequence similarity [21]. According to phylogenetic analysis, all Bangladesh strains belonged to the NiV-BD lineage and were separated into two sublineages, NiV-BD 1 and NiV-BD 2, both found in isolates from humans and bats [10,20,22].

Epidemiology of NiV

There is a distinct seasonal pattern in the epidemiology of NiV infection, with increased transmission in areas where people and fruit bats come into close contact, especially when humans consume date palm sap tainted with bat excreta [8,23]. Moreover, documented Human-to-human transmission in healthcare settings further heightens the outbreak potential and public health risks [13,24]. Table 1 documents the outbreaks [25].

Table 1. Global Timeline of Reported NiV Outbreaks. Transmission Patterns and Case Fatality Rates.

Year	Period	Country	Specific Location	Cases	Deaths	CFR (%)	Transmission / Source	Key Notes
1998–1999	Sep 1998 – May 1999	Malaysia	Perak, Negeri Sembilan, Selangor	265	105	~40	Pig-associated zoonosis	First recognized outbreak; initially misdiagnosed as Japanese encephalitis
1999	—	Singapore	—	11	1	~9	Imported from Malaysia	Linked to the Malaysian outbreak
2001	Jan 31 – Feb 23	India	Siliguri	66	—	74	Person-to-person	~75% hospital-linked transmission
2001	Apr – May	Bangladesh	Meherpur District	13	9	69	Likely zoonotic	Early Bangladesh cluster
2003	Jan	Bangladesh	Naogaon District	12	8	67	—	Seasonal recurrence
2004	Jan – Feb	Bangladesh	Manikganj & Rajbari	42	14	33	Close contact	Community spread
2004	Feb 19 – Apr 16	Bangladesh	Faridpur District	36	27	75	Person-to-person	ARDS has been reported in humans
2005	Jan	Bangladesh	Tangail District	12	11	92	Date palm sap contamination	Fruit bat exposure suspected
2007	Feb – May	India	Nadia District	up to 50 suspected	3–5	—	Person-to-person	Cross-border cluster with Bangladesh
2008	Feb – Mar	Bangladesh	Manikganj & Rajbari	9	8	89	Close contact	Continued endemic activity
2010	Jan	Bangladesh	Bhanga, Faridpur	8	7	88	Healthcare exposure	Physician's death reported
2011	Feb	Bangladesh	Hatibandha, Lalmonirhat	—	21	—	Fruit contamination	School cluster; schools closed
2018	May	India	Perambra, Kozhikode, Kerala	—	21	—	Person-to-person suspected	Ribavirin used
2019	Jun – Jul	India	Kochi/Ernakulam, Kerala	1	0	0	Isolated case	Large-scale contact tracing (338 monitored)
2021	Sep	India	Kozhikode, Kerala	1	1	100	Close contact	Healthcare workers symptomatic
2023	Jan – Feb	Bangladesh	—	11	8	73	—	WHO: national risk is high
2023	Sep	India	Kozhikode, Kerala	5	2	40	Close contact	>700 contacts traced
2024	Jul	India	Malappuram, Kerala	1	1	100	—	60 contacts identified
2026	Jan	India	West Bengal	5	—	—	Healthcare-associated	

Malaysia/ Singapore

NiV was initially isolated in September 1998 after a respiratory and encephalitis outbreak among Malaysian pig farmers and people who had close contact with pigs [26]. Early in the outbreak, four

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patients tested positive against IgM antibodies of Japanese Encephalitis (JE), leading to an initial diagnosis of JE. Despite the use of JE-directed control measures, transmission continued to escalate. By late 1998, additional clusters emerged in the Port Dickson District, approximately 300 km south. A novel virus (NiV) was discovered in March 1999 in cerebrospinal fluid (CSF) from a patient in Sungai Nipah village. Ultimately, this Malaysian outbreak resulted in 283 cases of acute encephalitis and 109 deaths, introducing NiV to the scientific community and highlighting its epidemic potential [27]. The outbreak predominantly affected pig farmers and those who were in direct contact with infected pigs, leading to large-scale culling of more than a million pigs to halt further spread [2,28]. Around the same period, an outbreak involving 11 cases and one death was reported among slaughterhouse workers in Singapore. Infections documented in Singapore were epidemiologically linked to the import of infected pigs from Malaysia, demonstrating transboundary transmission via commercial swine trade [29].

Bangladesh

In contrast to the Malaysian/Singapore outbreak, which was linked to infected pigs, the Bangladesh outbreaks are largely of repeated zoonotic spillovers from fruit bats [30]. These outbreaks are followed by secondary transmission within households and healthcare settings, contributing to consistently high case-fatality rates [31]. Since the first recognized outbreak in 2001, Bangladesh has emerged as the world's most persistent hotspot for NiV.[32,33]. The recurrent outbreaks in winter primarily affected 20 districts in central and north-western Bangladesh, which is commonly referred to as the 'Nipah belt' [34,35]. This zone represents the epicenter of the majority of the zoonotic spillover events, with a distinct epidemiological pattern [36,37]. In 2025, the NiV was identified for the first time in Bhola district, marking a notable geographical expansion of transmission; overall, infections have now been documented in 35 of Bangladesh's 64 districts. Historically, the highest infection and mortality burdens have been concentrated in Faridpur, Rajbari, Naogaon, and Lalmonirhat [37].

These outbreaks show a clear seasonal pattern, occurring between December and April, coinciding with the date palm sap-harvesting period. The most common way humans contract infections from bats is by consuming raw date palm sap. Date palms are often visited by pteropus bats, who suck the sap streams that are being collected. Additionally, bats may contaminate the sap collection pots with urine, feces, or saliva, which would allow viruses to spread [23,38,39]. The risk of environmental pollution and human infection is further raised during these times due to increased bat activity, which is the main source of zoonotic transmission, close to human settlements [40]. Surveillance data compiled by the World Health Organization, from 2001 to 2025, Bangladesh reported 357 laboratory-confirmed NiV infections and 241 deaths, corresponding to an overall case fatality rate of approximately 73%, underscoring the persistent and severe public health burden associated with seasonal spillover events [41].

More recently, on 3 February 2026, a NiV case was reported in Rajshahi Division. The patient initially developed fever accompanied by neurological manifestations on 21 January, and virological confirmation was obtained on 29 January. No recent travel history was documented; however, consumption of raw date palm sap was reported. A total of 35 close contacts were traced and tested negative for the NiV; they remain under surveillance. To date, no evidence of secondary transmission has been observed. These frequent seasonal outbreaks demonstrate that the NiV has become an endemic seasonal threat in Bangladesh, underscoring the critical need for long-term community-based prevention strategies, improved surveillance systems, and rapid diagnostic capabilities in high-risk areas [42].

India

India has experienced multiple, geographically distinct NiV outbreaks over the past two decades. In Siliguri, West Bengal, the first outbreak was recorded in 2001, resulting in 66 probable

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cases and 45 fatalities. The lack of functional laboratories during the first outbreak prevented timely screening, which was associated with a high case fatality rate [43]. The following outbreak happened in 2007 in Belechuapara village in West Bengal's Nadia district. The public health department was concerned since five individuals were seriously impacted and all of them died within a week of contracting the infection, showing a 100% CFR [44,45]. These outbreaks occurred near the boundary of Bangladesh's Nipah belt. Infection was primarily linked to consumption of bat-contaminated date palm sap, with subsequent human-to-human transmission driving further spread. The circulating lineage was NiV-Bangladesh (NiV-BD), characterized by comparatively lower transmissibility but a markedly high fatality rate [44,46].

A major epidemiological shift was observed in 2018, when NiV emerged for the first time in southern India, affecting Kozhikode and Malappuram districts of Kerala, causing 23 cases with approximately 91% mortality [47–49]. Following the 2018 outbreak, the Government of Kerala substantially strengthened public health preparedness and rapid response systems, a strategy reflected in 2019 when transmission was contained to a single index case with zero fatalities [44]. Later in 2021 and 2023, outbreaks in the Kozhikode district of Kerala reported 3 cases with 33% case fatality rate and 8 cases with 25% case fatality rate, respectively, demonstrating progressively improved outcomes [44]. Likewise**, in 2024,** Kerala **reported two confirmed NiV cases, both of which resulted in fatalities. Between May and July 2025, four laboratory-confirmed cases were documented in** Malappuram **and** Palakkad **districts of Kerala, with two associated deaths [50].** Most recently, in January 2026, two laboratory-confirmed NiV infections were reported among healthcare workers in North 24 Parganas, West Bengal; extensive contact tracing identified no additional cases, reflecting enhanced outbreak preparedness and response. Collectively, these events illustrate India's evolving NiV landscape from high-fatality, poorly characterized early outbreaks to more rapidly contained clusters, emphasizing the critical role of early detection, rigorous infection control, and sustained One-Health surveillance [51].

Philippines

In 2014, the NiV emerged as a zoonotic outbreak on Mindanao Island in the Philippines [52]. A total of seventeen cases were confirmed, and the fatality rate was 82%. Epidemiological investigation revealed that ten patients had direct exposure to horses or had consumed horse meat before the onset of illness. Ten horses died during the same period, among which nine had neurological symptoms. However, diagnostic testing for the NiV was not performed on the horses' samples. Although the source of horse infection was unclear, spillover from fruit bats was identified as the most likely source [53,54]. Five patients, including two healthcare personnel, acquired the disease through human-to-human transmission, highlighting the virus's capacity for nosocomial spread and amplification within a clinical setting [27]. This strain was related to the Malaysian lineage, which previously lacked confirmed human-to-human transmission, suggesting viral co-evolution within bat reservoirs and the likelihood of mutations arising from repeated spillover events [27].

Reservoir and Mechanism of Transmission of NiV

Epidemiological data reveal that the NiV has multiple, direct routes of transmission [2,55]. Most infections arise from sporadic and zoonotic spillover events, and cross-species transmission is especially by reservoir fruit bats [56,57]. Exposure particularly occurs through the consumption of bat- contaminated food products, although other mammals may also act as intermediate hosts [58]. Fruit bats of the genus *Pteropus,* also known as flying foxes, act as the natural reservoir, maintaining the virus in nature while remaining largely asymptomatic [59]. These bats are extensively dispersed throughout South and Southeast Asian nations, as well as Australia, East Africa, and a large number of oceanic islands in the Pacific and Indian oceans, all of which closely correlate with frequent human outbreaks [11]. The virus shedding occurs intermittently through bat saliva, urine, feces, and partially

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eaten fruits, leading to environmental contamination [60]. Human infection commonly follows consumption of contaminated date palm sap or related products [13]. During the initial outbreak in Malaysia, pigs served as the principal amplifying host, facilitating rapid transmission to farmers and prompting substantial reforms in livestock management practices [61,62].

On the other hand, the epidemiological features of the NiV in Bangladesh and India differ from those in Malaysia and Singapore, with significant variations in fatality rates and transmission patterns [63]. Transmission of viral infection in Bangladesh and India is frequently due to the consumption of bat-contaminated raw date palm sap [6,64]. Human-to-human transmission has become a crucial mode in these settings, affecting healthcare professionals and close household contacts through exposure to respiratory and other body fluids [13,65]. In Bangladesh, cultural customs related to post-mortem care have also aided in transmission [66,67]. Healthcare-associated clusters have been observed repeatedly in India, starting with the Siliguri epidemic in 2001 and continuing with later outbreaks in Kerala, in which direct contact with infected patients facilitated transmission [43,68]. These observations highlight distinct regional transmission dynamics and emphasize the growing importance of nosocomial and community-based amplification in maintaining NiV outbreaks.

Pathogenesis

NiV is transmitted by direct contact with damaged skin or mucosal surfaces, ingestion of infected material, and inhalation of respiratory droplets or aerosols [7] (Figure 1). To facilitate membrane fusion and intracellular entry, virus surface glycoproteins bind to ephrin-B2/B3 receptors on epithelial cells in the respiratory system [69]. After local replication, the virus spreads hematogenously, affecting endothelial cells in the brain, kidneys, gastrointestinal tract, lungs, and other organs [70]. Neuroinvasion is contributed to by both vascular pathways involving the choroid plexus and the cerebral microvasculature, as well as retrograde axonal transport along the olfactory pathway. When the central nervous system is involved, the blood–brain barrier is compromised, which encourages the release of pro-inflammatory mediators, including interleukin-1β and tumor necrosis factor-α, which lead to neurological symptoms [71]. Simultaneously, airway epithelial infection triggers a strong inflammatory cascade marked by increased levels of granulocyte colony-stimulating factor, IL-1α, IL-6, IL-8, and CXCL10, which results in the recruitment of immune cells and acute lung damage that resembles ARDS [72]. As systemic spread occurs, virions either move freely or attach to host leukocytes. Viral replication is accompanied by increased expression of non-structural proteins (notably V and C), which antagonize host interferon responses and facilitate immune evasion, thereby amplifying viral propagation and multisystem involvement [73,74].

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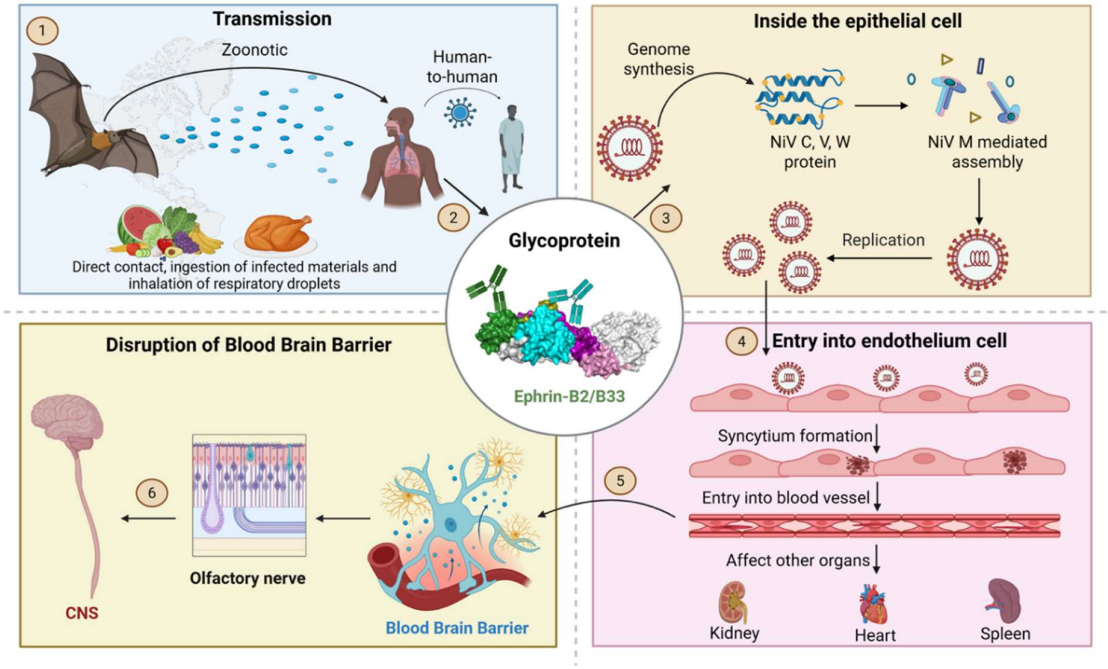

Figure 1. Pathogenesis of NiV Infection: Cellular Entry, Systemic Dissemination, and Neuroinvasion.

Clinical Manifestations and Disease Progression

NiV infection in humans has a variable incubation period, commonly ranging from 4 to 21 days, although longer timeframes up to 2 months have also been reported in some studies [75,76]. 90% of infected individuals experience clinical symptoms within 2 weeks of exposure, with an average time to onset of 10 days (Table 2) [77]. Early infection with NiV typically begins with **nonspecific symptoms** such as fever, headache, cough, sore throat, vomiting, and dizziness, breathing difficulties which can make early clinical diagnosis difficult because these features resemble many other febrile illnesses progressing to severe symptoms which are frequently linked to fatigue, disorientation, drowsiness, confusion, seizures, and even coma, often associated with encephalitis and brain swelling [8,12,13] (Figure 2).

Table 2. Differential diagnosis of Nipah virus infection: clinical features, epidemiological clues, and diagnostic approaches.

Disease	Main overlapping features with NiV	Distinguishing clinical / epidemiologic clues	Suggested confirmatory tests
Nipah virus (NiV)	Acute febrile illness, encephalitis, seizures, altered mental status, severe respiratory disease/ARDS	Exposure to bats, pigs, or contaminated food (e.g., date palm sap); person-to-person transmission; high CFR; outbreaks in South/Southeast Asia	RT-PCR (respiratory samples, CSF, blood), IgM/IgG ELISA, virus isolation (BSL-4)
Japanese encephalitis (JE)	Fever, headache, seizures, encephalitis	Mosquito exposure, rural settings, less respiratory involvement	JE IgM (serum/CSF), PCR
Herpes simplex encephalitis (HSE)	Fever, encephalopathy, seizures	Sporadic cases, focal neurologic signs, temporal lobe involvement	CSF HSV PCR, MRI, EEG
Cerebral malaria	Fever, confusion, seizures, coma	Travel to endemic areas, anemia, thrombocytopenia	Blood smear, rapid antigen test

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Leptospirosis	Fever, myalgia, multiorgan involvement	Conjunctival suffusion, exposure to contaminated water	PCR (early), IgM serology/MAT
Scrub typhus	Fever, headache, pneumonitis	Eschar, rural exposure, lymphadenopathy	Serology, PCR
Dengue	Fever, myalgia, thrombocytopenia	Rash, retro-orbital pain, plasma leakage	NS1 antigen, PCR, serology
Chikungunya	Fever, headache, rash	Severe joint pain/arthritis	PCR, serology
Avian influenza (H5N1)	Fever, cough, severe respiratory illness	Contact with poultry, respiratory predominance	RT-PCR influenza
Hendra virus infection	Fever, encephalitis, respiratory disease	Exposure to horses, Australia	RT-PCR, serology

Neurological involvement becomes more noticeable as the disease progresses; symptoms include abnormal pupillary reflexes, sensory abnormalities, vasomotor changes, and myoclonus. In certain cases, these symptoms may present as focal involvement of the medulla oblongata, diffuse encephalitis, or meningitis [2,12]. Concurrently, respiratory manifestations are observed in the patient, initially presenting with fever, cough, dyspnea, and muscle pain, and may subsequently progress to atypical pneumonia, presenting with shortness of breath, rapid breathing, and radiographic evidence of lung infiltration. Patients may experience acute respiratory distress syndrome (ARDS) in extreme circumstances, necessitating mechanical breathing [78,79]. Nipah–Bangladesh infections are more frequently associated with prominent respiratory involvement compared with Nipah–Malaysia strains, whereas neurological manifestations remain a consistent hallmark across all NiV variants [10,80].

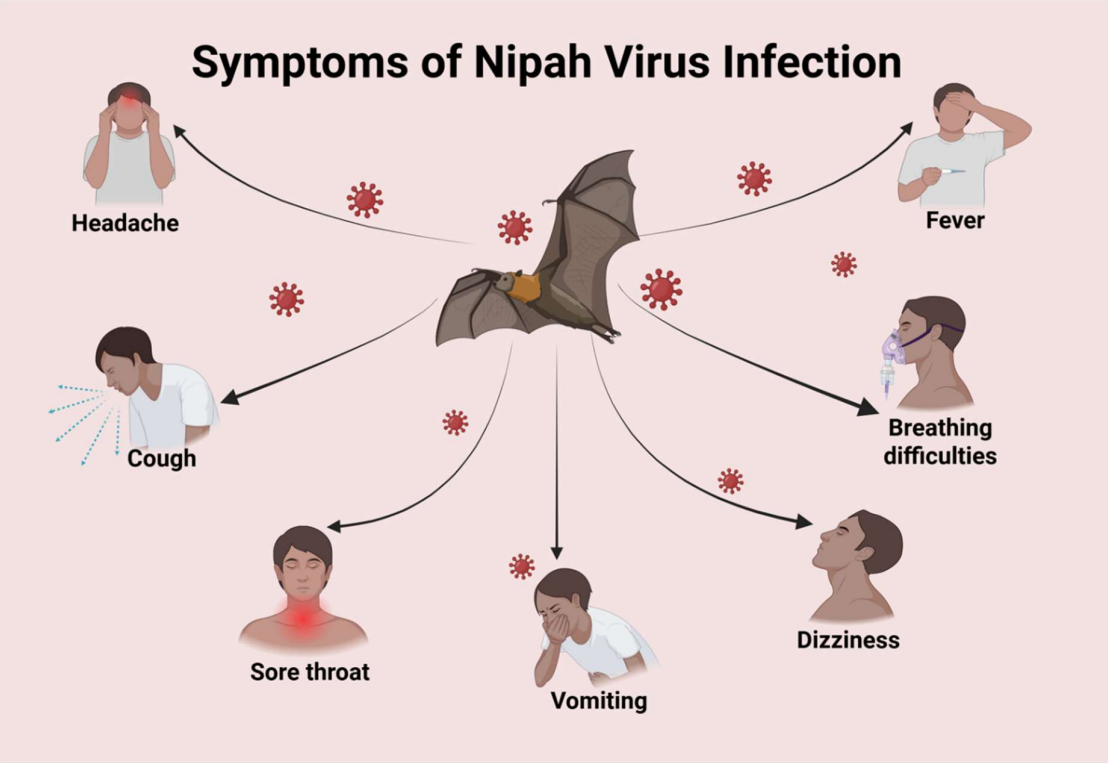

Figure 2. Clinical Spectrum of NiV Infection: Major Signs and Symptoms.

Beyond the central nervous system, severe cases can also damage other organs like the kidneys, pancreas, and heart [8]. Among survivors, especially those with encephalitic presentations, **persistent**

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neurological and functional impairment has been documented. Longitudinal follow-up studies reported that **neurologic sequelae were common, may persist for years;** importantly, **neurologic dysfunction may develop even after recovery from the acute illness** [81,82]. Depending on the particular infecting NiV strain, up to 11% of infected people may stay asymptomatic, yet the mortality rate of NiV infection varies from 40% to 75% [83]. Rapid progression to encephalitis and convulsions in fulminant cases frequently results in coma within 24 to 48 hours, indicating a dismal prognosis. Death usually happens within a median of 6 days after the onset of symptoms [79,84].

NiV infection presents with a broad and often nonspecific clinical spectrum, ranging from acute febrile illness to rapidly progressive encephalitis and severe respiratory disease, which can overlap with multiple infectious conditions. In endemic and outbreak settings, this overlap poses significant diagnostic challenges, particularly during the early stages of illness. Key differential diagnoses include viral encephalitides such as Japanese encephalitis and herpes simplex encephalitis, as well as systemic and zoonotic infections, including cerebral malaria, leptospirosis, scrub typhus, dengue, chikungunya, and zoonotic influenza viruses. Distinguishing these conditions relies on a combination of epidemiological context, clinical features, and targeted laboratory testing. A comparative summary of Nipah virus infection and its principal differential diagnoses is provided in Table 2.

NiV, Nipah virus; JE, Japanese encephalitis; HSE, herpes simplex encephalitis; ARDS, acute respiratory distress syndrome; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalogram; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; IgG, immunoglobulin G; MAT, microscopic agglutination test; CFR, case fatality rate; BSL-4, biosafety level 4.

Laboratory Diagnosis

Timely and accurate laboratory diagnosis is important for the early detection and containment of NiV outbreaks. Because of substantial clinical overlap with other etiologies of acute febrile encephalitis and severe respiratory disease, laboratory confirmation is required [83]. Blood, throat/nasal swabs, urine, and cerebrospinal fluid samples should be taken from infected humans and animals as soon as possible for clinical diagnosis [21,27]. Although virus propagation mandates biosafety level-4 (BSL-4) containment, initial virus isolation from suspected clinical specimens may be performed in biosafety level-3 (BSL-3) facilities, provided enhanced containment measures are in place [8]. IgG/IgM/antigen ELISA, immunofluorescence assay, histopathology, virus isolation and neutralization, and nucleic acid amplification testing (NAAT, such as PCR and sequencing) are all used in laboratory confirmation of NiV infection [83].

Real-time reverse transcription PCR (RT-PCR) is the most sensitive technique for early detection of active NiV infection, while NiV-specific IgM ELISA serves as a valuable complementary serological tool, particularly in resource-limited settings where molecular diagnosis is unavailable [83]. IgM ELISA is a valuable tool for diagnosing recent or acute infections. In contrast, IgG ELISA is primarily used in sero-epidemiological surveillance, with IgG positivity indicating the convalescent phase in recovered individuals. The specimens required for the ELISA test include serum or plasma, although cerebrospinal fluid can be used in suspected encephalitis cases [21]. Histopathology, combined with immunohistochemistry, can be used to confirm NiV infection in fatal cases after death. Although virus isolation and neutralization tests offer conclusive confirmation, they are only carried out in Biosafety Level-4 laboratories due to the stringent safety and containment requirements [83].

Treatment and Clinical Management

The NiV has been designated a priority disease by the World Health Organization (WHO) due to its high pandemic potential. Clinical management of NiV infection primarily relies on supportive care and public health measures, as there are no approved vaccines or licensed antiviral therapies

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[33,85]. Early admission to high-dependency or intensive care units is often necessary for patients to receive supplemental oxygen or mechanical ventilation in respiratory failure or acute respiratory distress syndrome (ARDS), hemodynamic stabilization with prudent fluid resuscitation, vasopressors for shock, and airway protection. Neurological treatment focuses on seizure control, reduction of intracranial pressure, and metabolic optimization in acute encephalitis. Acute kidney injury may necessitate renal replacement therapy, and empirical antibiotics are only started when a subsequent bacterial infection is detected [86]. Though ribavirin and favipiravir have shown variable or preclinical activity, and investigational monoclonal antibodies such as m102.4 appear promising [87]**.** According to the World Health Organization's recommendations, strict preventive measures, such as prompt patient isolation, proper use of personal protective equipment, committed care teams, and thorough environmental decontamination, are crucial for preventing nosocomial transmission [88]. Among survivors, persistent or delayed neurological sequelae, including cognitive impairment, seizures, and relapsing encephalitis, are frequently reported [81,89]. Clinical management remains challenging, especially in endemic, resource-limited settings, due to inadequate intensive care capacity, delayed diagnosis, and workforce constraints. Until disease-specific treatments become available, improved outcomes will require an early diagnosis, high-quality supportive care, strict infection control, and coordinated public health interventions integrated within One Health frameworks.

Vaccines

Despite the lack of approved human NiV vaccinations, there is compelling evidence that a successful vaccine is possible [90]. Multiple vaccine strategies targeting **NiV** have been developed, with several advancing to evaluation in diverse animal models. Multiple vaccine platforms have established that the NiV surface glycoproteins—the attachment glycoprotein (G) and fusion protein (F)—either alone or in combination, act as potent immunogens, eliciting robust neutralizing antibody responses and protective immunity in preclinical models. [90]. Due to the high pathogenicity of the NiV, the live-attenuated vaccine with no reversion potential remains challenging. However, recombinant attenuated NiV mutants have demonstrated strong neutralizing antibody responses in hamster and ferret models [90]. A subunit vaccine targeting the G glycoprotein (sG) of NiV and HeV is the most studied strategy. It is noteworthy that HeV-sG produces a cross-protective immunological response against both HeV and NiV. Equivac, a horse vaccination against HeV, is registered in Australia [17]. Virus vector-based recombinant vaccines have been developed. These recombinant viruses express the F or G glycoproteins on their surface. Additionally, a vaccine composed of virus-like particles produced in mammalian cells has been developed [91–93]. Collectively, these strategies have conferred total defense against the oro-nasal NiV challenge following a single immunization across multiple animal models. Notably, the demonstrated efficacy of the sG vaccine in horses and the rVSV-ZEBOV platform underscores the translational potential of these approaches, positioning them as promising candidates for eventual evaluation in humans [90]. Table 3 documents vaccine trials [94].

Table 3. Pipeline of NiV Vaccine Candidates and Ongoing Clinical Trials.

NCT Number	Phase/Type	Intervention	Status	Country
NCT05398796	Dose escalation	mRNA vaccine	Completed	USA
NCT06221813	Phase 1	PHV02 vaccine	Completed	USA
NCT04199169	Phase 1	HeV-sG-V vaccine	Completed	USA
NCT05178901	Phase 1	PHV02 vaccine	Completed	USA
NCT01811784	Community prevention	Behavioral	Unknown	Bangladesh

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Prevention and Control Measures

NiV is acquired by humans primarily through fruit bats and is further amplified by healthcare-associated spread, particularly in Bangladesh and India [14]. Rapid isolation of suspected cases, quarantine and symptom monitoring of close contacts, and stringent Effective outbreak control requires both infection prevention and control strategies, including the use of the appropriate personal protective equipment [49,95]. Limiting zoonotic transmission requires avoiding close contact with pigs, bats, and possibly infected food. Covering the sap-collecting areas of date palm trees with clothes helps to prevent bats from touching the sap, which reduces the risk of contamination [27]. Robust surveillance systems, such as early case detection, laboratory confirmation, contact tracing, and active follow-up during the incubation period, enable timely containment. A One Health strategy that incorporates environmental, animal, and human surveillance offers early warning by monitoring bat populations, investigating unusual animal deaths, and identifying high–risk human–animal interfaces [96]. Until effective vaccines or targeted therapies are widely accessible, prevention depends on proactive surveillance, community education, strict infection control, improved health systems, and continued multisectoral collaboration supported by ongoing research.

Public Health Challenges of Niv

NiV continues to pose a major and persistent threat to public health because of its unexpected spillover from fruit bats and its high mortality [65]. Outbreaks frequently occur abruptly without clear warning because bats shed the virus intermittently, making prevention difficult. Since the early symptoms are vague and mimic those of common feverish illnesses, diagnosis is delayed, allowing transmission in households and healthcare settings. Healthcare-associated transmission is still a major public health concern in India and Bangladesh. Human, animal, and environmental interactions, such as deforestation, farming practices, and consumption of raw date palm sap, significantly impact transmission, underscoring the importance of a One Health approach. Coordinated regional surveillance is necessary for cross-border transit between neighboring countries. Finally, lack of funding, logistical difficulties, and poor commercial incentives slow research and development of effective vaccines and therapeutics, emphasizing the need for sustained investment in preparedness and global collaboration

Future Directions

Future research on the NiV should focus on preventing epidemics before they occur and improving preparedness when they do. A strong One Health approach that integrates human, animal, and environmental health is essential to prevent future spillovers and improve vaccine efficacy across populations [97]. Enhancing global collaboration through WHO-supported funding and training will strengthen surveillance and outbreak management [65]. Vaccine and treatment development should also be strengthened by prioritizing future research to develop vaccines using multi-epitope and viral vector-based strategies [65]. Outbreak preparedness must improve at the regional level. This includes expanding laboratory networks with field-deployable molecular diagnostics, strengthening infection prevention and control (especially during aerosol-generating procedures), building referral systems for severe neurological cases, and conducting regular joint simulation exercises between animal and human health sectors [98]. Finally, climate change should be considered a key research priority. Changes in temperature, rainfall, fruiting seasons, and bat migration patterns may alter viral shedding and the risk of human exposure. Long-term studies linking climate factors with bat behavior and spillover events are necessary to develop climate-informed risk maps and guide preventive policies [99].

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Limitations

This review has several limitations that should be acknowledged. First, although a comprehensive search strategy was applied across multiple databases, this work does not constitute a formal systematic or scoping review; therefore, selection bias and incomplete retrieval of all relevant studies cannot be excluded. Second, the available evidence on NiV infection is heterogeneous and largely derived from outbreak reports, observational studies, and case series, often from limited geographic regions such as South and Southeast Asia. This may restrict the generalizability of findings to other settings where surveillance remains limited or absent. Third, variability in diagnostic capacity, reporting standards, and case definitions across outbreaks may have influenced the accuracy and comparability of epidemiological and clinical data. Additionally, publication bias toward severe or unusual cases may overrepresent the most critical clinical manifestations and outcomes. The rapidly evolving nature of emerging infectious diseases, including the NiV, also implies that some information may become outdated as new data emerge. Finally, while supportive evidence synthesis tools were used, their outputs depend on the quality and availability of underlying data. Despite these limitations, this review provides a comprehensive and clinically relevant synthesis of current knowledge and highlights key areas requiring further research.

Conclusions

The NiV still poses a major risk to community well-being, public health, and economic stability, especially in areas where zoonotic spillover is common. Despite significant progress over the past two decades in understanding viral pathogenesis and transmission, the absence of licensed therapies or vaccines makes prevention and control difficult. Effective preparedness relies on early case detection, prompt isolation, strong surveillance systems, and strict infection-control practices, supported by sustained community awareness. The close interface between fruit bats, environmental change, and human activity underscores the urgent need for integrated One Health strategies. Continued research on viral biology, immune evasion, transmission dynamics, and emerging variants is essential for vaccine and therapeutic development. Finally, coordinated national and international efforts, strong public health funding, and community involvement are important for reducing future outbreaks and strengthening pandemic preparedness.

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