Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2024, 15, 161-173
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

Nipah Virus Unveiled: A Review Article

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How to cite this paper: Magdum, M., Chowdhury, Md.A.T., Khandaker, M., Datta, R., Rayhan, Md.N., Uddin, Md.S., Bhuiyan, Md.J.I., Ahaduzzaman, Md., Kabir, Md.A.A.-M., Uddin, M.Z., Sahid, Md.E.U. and Saha, S. (2024) Nipah Virus Unveiled: A Review Article. *Advances in Bioscience and Biotechnology*, **15**, 161-173.
https://doi.org/10.4236/abb.2024.153011

Received: January 27, 2024
Accepted: March 12, 2024
Published: March 15, 2024

Abstract

Nipah virus (NiV) is a highly infectious zoonotic pathogen that poses a significant threat to human and animal health. First identified in Malaysia in 1998, NiV has since caused several outbreaks in Southeast Asia, with sporadic cases reported in Bangladesh and India. The virus is primarily transmitted to humans through direct contact with infected animals, primarily fruit bats, or through the consumption of contaminated fruits and their juices. NiV infection presents a wide spectrum of clinical features, ranging from mild respiratory illness to severe encephalitis, with a high case fatality rate. The incubation period typically ranges from 4 to 14 days, during which patients develop fever, headache, myalgia, and respiratory symptoms such as cough and sore throat. As the disease progresses, neurological signs become prominent, including altered consciousness, seizures, and focal deficits. Severe cases may exhibit acute respiratory distress syndrome and multi organ failure. Laboratory findings often include lymphocytopenia, thrombocytopenia, and elevated liver enzymes. Diagnosis of NiV infection requires specialized laboratory testing, including reverse transcription-polymerase chain reaction (RT-PCR) and serological assays. Currently, no specific antiviral treatment exists for NiV infection, and management primarily focuses on supportive care. Prevention and control strategies encompass public health interventions, surveillance, and raising awareness among healthcare providers and the general population. The emergence and re-emergence of NiV highlight the urgent need for continued research, improved diagnostic capabilities, and the

development of effective vaccines and therapeutics to mitigate the impact of this deadly virus.

Keywords

Nipah Virus, Zoonotic Pathogen, Outbreaks, Surveillance

1. Introduction

Nipah virus (NiV), an RNA virus classified in the Paramyxoviridae family and Henipavirus genus alongside the Hendra virus (HeV) and Cedar virus, finds its natural reservoir in bats [1]. Although Cedar virus exhibits no pathogenicity in animals, NiV and HeV are notorious for causing severe, potentially fatal neurological and/or respiratory diseases [2]. Recognizing its outbreak potential, the World Health Organization (WHO) has listed NiV among the pathogens demanding urgent research and development activities [3]. First emerging in Malaysia in 1998, NiV has since triggered multiple outbreaks in South and Southeast Asia, posing a significant threat due to its high pathogenicity across various mammalian species.

Addressing the challenges posed by NiV necessitates comprehensive strategies. Furthermore, adopting a One Health approach is imperative, considering the interconnectedness between humans, domestic and peri-domestic animals, and the environment [4]. NiV's ability for zoonotic transmission and person-to-person spread adds complexity to containment efforts [4]. Pteropus bats, the primary reservoir of NiV, exhibit a global distribution, raising concerns about potential spill-over events in new geographical areas where these bats reside.

An integrated "One Health" strategy encompassing humans, household, and surrounding animals, alongside the ecosystem, is essential for effectively managing the disease. Urgent research is required to investigate epidemiology, modes of transmission, and potential prevention and control.

2. Methods

A comprehensive literature search was conducted using digital archives, including PubMed, Google Scholar, and the Cochrane Library. The search utilized a combination of MeSH terms related to Nipah virus infection, encompassing aspects such as epidemiology, clinical features, diagnosis, surveillance, vaccines, and specific geographical regions. The search encompassed literature reviews, original research papers, case reports, and relevant cross-references. Additionally, epidemiological reports from reputable organizations such as the WHO and the NCDC were included. The aim was to gather information on Nipah virus transmission, diagnosis, and control strategies.

3. Epidemiology

Malaysia: Human NiV infection was first identified in Malaysia from 1998 to 1999 [5]. The name "Nipah" comes from Sungai Nipah (Nipah River village). Several cases presenting with fever, headache and reduced consciousness were reported from the state of Perak, Malaysia in September 1998. Initially, four cases tested positive for IgM antibodies against Japanese Encephalitis (JE) and a JE outbreak was declared. Despite the implementation of control measures, the outbreak intensified. By the end of the year, more clusters were reported in Port Dickson District, 300 km south [6]. In March 1999, a new virus (NiV) was isolated from the cerebrospinal fluid (CSF) of a patient from Sungai Nipah village [7]. Eventually, the outbreak caused 283 symptomatic cases and 109 deaths [5]. In March 1999, an outbreak (11 cases, one death) was reported from Singapore among slaughterhouse workers [8]. In these outbreaks, close contact with pigs or pig excreta was shown to be a risk factor [8] [9]. The infected animals themselves showed mild respiratory illness. In Malaysia, large numbers of animals are raised together in pig farms/slaughterhouses, where the outbreak began and animal to animal spread is likely. Culling of over a million pigs followed by disposal by deep burial and decontamination with quick lime, along with other control strategies was successful in controlling the outbreak [10]. Dogs were also found to be commonly infected [11] and dogs dying on farms were found to be another risk factor [9]. There is no evidence of human-to-human transmission from these outbreaks. Eventually, Pteropus bats were shown to be the reservoir of infection in Malaysia [12] which infected the amplifying hosts, pigs, through the consumption of bat-bitten fruit.

Bangladesh: The epidemiology of NiV is significantly different in Bangladesh. Since 2001, seasonal outbreaks of NiV have occurred in Bangladesh in winter months, primarily in 20 districts in central and north-western Bangladesh (the Nipah belt), where majority of spillover events occur [6]. Pteropus bats have been identified as the reservoir [13]. Transmission is Bangladesh may occur through various routes. Drinking raw date palm sap is the most common form of transmission of infection from bats to humans [14]. Outbreaks coincide with sap harvesting season (December-May). Pteropus bats have been found to visit date palm trees and lick the sap streams being used for collection. Bats may also contaminate the sap collection pots with urine or faeces [15]. Domestic animals may also serve as a route of transmission from bats to humans. Person to person spread is an important mode of transmission in Bangladesh and has been identified in all outbreaks. Consumption of bat bitten fruit has also been suspected of being a potential mode of transmission, through definitive evidence has so far been elusive. The primary modes of transmission in Bangladesh have been found to be date palm sap consumption and person to person transmission [16]. Since 2001, Bangladesh has been reporting seasonal outbreaks of Nipah virus infection between December and May, corresponding with the harvesting season of date palm sap (DPS) zero (in 2002, 2006 and 2016) to 67 (in 2004). A lower number

of reported cases were observed from 2016 following an extensive advocacy campaign against the consumption of raw date palm sap.

However, between 4 January to 13 February 2023, a total of 11 (ten confirmed and one probable) cases of Nipah virus infection including eight deaths (CFR 73%) were reported from seven districts across two divisions in Bangladesh. This is the highest number of cases since 2015 when 15 cases including 11 deaths were reported. Ten of the 11 reported cases were laboratory confirmed, while samples could not be collected from one case before death and is therefore considered a probable case based on epidemiological linkage. Laboratory confirmation of Nipah virus infection was carried out through Real Time Polymerase Chain Reaction (RT-PCR) using samples from throat swabs and antibody detection via enzyme-linked immunosorbent assay (ELISA). Confirmatory tests were done at the Institute of Epidemiology, Disease Control and Research (IEDCR) and International Centre for Diarrhoeal Disease Research, Bangladesh, (ICDDR, B) laboratories. Six cases were reported from Dhaka Division including four deaths from the districts of Narsingdi (one case who died), Rajbari (four cases including three deaths) and Shariatpur (one case). Rajshahi Division reported five cases including four deaths from the districts of Naogaon (two cases including one death), Natore (one case who died), Pabna (one case who died), and Rajshahi (one case who died) (**Figure 1**) [17].

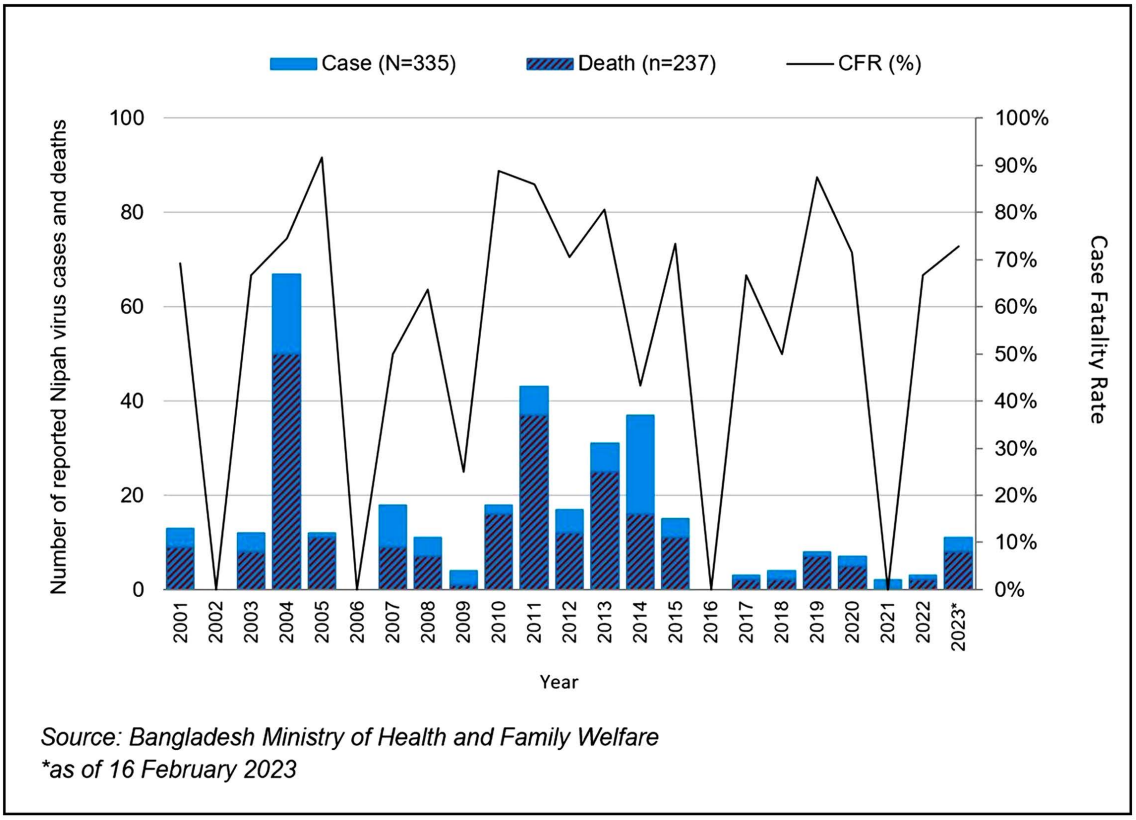

Figure 1. Illustrates the Nipah virus cases and deaths reported in Bangladesh from January 1, 2021, to February 13, 2023.

India: In India, there was a large outbreak (66 probable cases and 45 deaths) in Siliguri, West Bengal, in 2001 and another smaller outbreak (five points, 100% fatality) in 2007 in Nadia district, West Bengal. These outbreaks were across the border from the Nipah belt in Bangladesh. In May 2018, a flurry of NiV was declared in Kozhikode and Malappuram districts of Kerala, a southern state on the west coast, which is geographically disconnected from previously affected areas. Date palm sap consumption is rare in this area. There were 18 confirmed cases and 17 deaths as of 1 June 2018 [3]. All cases belonged to the economically productive age group, with no sex differential [18]. In 2001 in Siliguri, the index case remained unidentified but was admitted to Siliguri District Hospital and infected 11 secondary subjects. All patients at the hospital. These patients were transferred to other hospitals, and further transmission infected 25 staff and eight visitors [19]. The 2007 outbreak consisted of one person who contracted the disease due to consumption of alcohol made from the date palm, and all the others, including one healthcare worker, acquired the disease from the first case [20]. At least one healthcare professional also contracted the disease in a healthcare setting in the recent outbreak in 2018 [21]. All Indian episodes have seen person-to-person transmissions. Though the epidemiology of NiV in India is similar to Bangladesh, since only three outbreaks have been reported so far, definitive evidence is unavailable.

4. Pathogenesis

Henipaviruses, including the Nipah virus (NiV), have been extensively studied to unravel their pathogenic mechanisms. Molecular scrutiny of NiV's polymerase gene and genomic termini has yielded profound insights into its genetic architecture and replication mechanisms [22]. The P gene products of NiV exhibit distinct yet interwoven functions in manipulating the antiviral response of human endothelial cells [23]. Pathological investigations have brought to light the intricacies of NiV infection, underscoring its emergence as a zoonotic paramyxovirus [24].The expression of ephrins and Eph receptor tyrosine kinases in the central nervous system assumes significance in NiV invasion, given their involvement in dynamic cell adhesion and repulsion processes [25] [26]. Host-specific ephrin-B ligands have been pinpointed as receptors for Henipaviruses, influencing their cellular tropism and infection dynamics [27]. Notably, in a porcine host, NiV invasion of the central nervous system has been documented, suggesting a potential entry route through olfactory nerves [28]. Demonstrably, NiV showcases its capacity to counteract the interferon response, with the V, W, and C proteins actively inhibiting interferon activity [29]. Nonetheless, it is noteworthy that interferon signaling persists and remains functional during Henipavirus infection of human cell lines, underscoring the intricate and dynamic interplay between the virus and the host immune system [30]. NiV has been isolated and molecularly identified from pigs, highlighting their role as a potential intermediate host and reservoir for the virus [31]. The coevolution of different

NiV strains with their respective reservoir hosts, bats, has likely contributed to variations in clinical and epidemiological features [32].

5. Clinical Features

The clinical features of Nipah virus infection can vary, ranging from asymptomatic or mild illness to severe respiratory distress and encephalitis. Clinical features are:

- Incubation period: The incubation period for Nipah virus infection is typically between 4 to 14 days, but it can range from 3 to 40 days [18].
- Fever: One of the early symptoms of Nipah virus infection is the onset of a high-grade fever. The fever is often accompanied by headaches and body aches.
- Respiratory symptoms: Nipah virus infection can cause respiratory symptoms, including cough, sore throat, and difficulty breathing. In severe cases, it can lead to acute respiratory distress, requiring mechanical ventilation.
- Encephalitis: Nipah virus is known to cause severe encephalitis, which is inflammation of the brain. Encephalitis symptoms include confusion, disorientation, drowsiness, and neurological signs such as seizures [19].
- Muscle pain: Patients infected with Nipah virus may experience muscle pain or myalgia, which can be generalized or localized.
- Gastrointestinal symptoms: Nausea, vomiting, and abdominal pain are common gastrointestinal symptoms associated with Nipah virus infection. Diarrhea may also occur.
- Respiratory distress: In severe cases, Nipah virus infection can cause progressive respiratory distress syndrome, leading to respiratory failure and death.
- Hematological abnormalities: Nipah virus infection may be associated with hematological abnormalities, including lymphocytopenia (reduced lymphocyte count) and thrombocytopenia (reduced platelet count) [20].
- It's important to note that the clinical features of Nipah virus infection can vary in severity, ranging from mild respiratory illness to severe encephalitis, with a high case fatality rate. It is essential to consult a healthcare professional or refer to reputable sources such as the World Health Organization (WHO) or the Centers for Disease Control and Prevention (CDC) for the most up-to-date and accurate information on Nipah virus.

6. Diagnosis

The diagnosis of Nipah virus (NiV) infection involves a combination of clinical evaluation, laboratory tests, and epidemiological information. Several diagnostic methods are used to detect NiV, including:

1) Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR): This technique detects the presence of NiV RNA in patient samples such as blood, respiratory secretions, cerebrospinal fluid, or tissue specimens [33].

2) Virus Isolation: NiV can be isolated and cultured from clinical specimens,

such as throat swabs, blood, or cerebrospinal fluid, using cell culture techniques [33].

3) Serological Tests: Serological assays, including enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA), are employed to detect antibodies against NiV in patient serum samples. IgM antibodies indicate recent infection, while IgG antibodies suggest past exposure or immunity [34].

4) Immunohistochemistry: This technique involves the detection of NiV antigens in tissue specimens, usually obtained from autopsies of fatal cases, using specific antibodies [24].

It is essential to perform these diagnostic tests in certified laboratories equipped with appropriate biosafety precautions due to the high pathogenicity of NiV.

7. Disease Control and Management

The management and control of Nipah virus involves a combination of public health measures, surveillance, case management, and research efforts. Here are some key aspects of managing and controlling Nipah virus:

- **Early Detection:** Establishing a robust surveillance system is crucial to detecting Nipah virus cases early. This includes active surveillance in healthcare facilities, monitoring of wildlife populations, and reporting of unusual illness patterns. Rapid identification and reporting of suspected cases allow for timely response and control measures.
- **Infection Prevention and Control:** Implementing strict infection prevention and control measures is essential to prevent the spread of Nipah virus within healthcare settings. This includes isolation of suspected or confirmed cases, use of personal protective equipment (PPE), hand hygiene, and disinfection of contaminated surfaces.
- **Contact Tracing:** Identifying and monitoring individuals who have come into contact with confirmed cases of Nipah virus is crucial for preventing further transmission. Contact tracing helps identify potential secondary cases and allows for early intervention and monitoring of exposed individuals.
- **Case Management:** Providing supportive care to Nipah virus patients is an important aspect of management. There is currently no specific antiviral treatment available for Nipah virus, so symptomatic and supportive care, including respiratory and organ support, is the mainstay of treatment.
- **Public Awareness and Education:** Raising public awareness about Nipah virus, its transmission, and preventive measures is vital. This includes educating the public about avoiding direct contact with infected bats, refraining from consuming raw date palm sap contaminated by bat saliva or urine, and practicing good hygiene measures.
- **Animal Surveillance and Control:** Nipah virus is believed to originate from bats, with intermediate hosts such as pigs playing a role in transmission to humans. Surveillance and control measures targeting these animal popula-

tions, including culling infected or at-risk animals, can help prevent spillover events.

- **Research and Vaccine Development:** Continued research into Nipah virus, including its epidemiology, transmission dynamics, and potential vaccines or therapeutics, is essential for better prevention and control. Development of effective vaccines and antiviral treatments can significantly enhance efforts to manage and control Nipah virus outbreaks.

It's important to note that the management and control strategies may vary depending on the specific context, resources available, and guidance from local and international health authorities. Close coordination between healthcare providers, public health agencies, and researchers is critical for an effective response to Nipah virus outbreaks.

Surveillance Strategies in Bangladesh: Regular disease surveillance is conducted in the Nipah belt in Bangladesh to effectively monitor and respond to potential outbreaks. This surveillance includes event-based and sentinel administration, with electronic media monitoring involving national news channels. Dedicated hotlines are established for healthcare personnel to promptly report suspected outbreaks or unexplained deaths. In cases of encephalitis clusters, defined as two or more cases occurring within 21 days and within half an hour's walking distance from each other [35]. A team of epidemiologists from the Institute of Epidemiology, Disease Control, and Research in Bangladesh investigates the identified clusters. Their investigations encompass identifying suspected human cases, potential animal sources of infection, behavioral factors contributing to the condition, and environmental contamination. Implementing surveillance as an integral part of disease management is crucial, not only in areas with previous outbreaks like India but also in other countries within the region.

Prevention: Preventing the transmission of the Nipah virus (NiV) involves implementing various measures to reduce exposure to infected animals and contaminated materials. Here are some key prevention strategies:

1) Avoiding Direct Contact: Minimize contact with bats, especially in areas where NiV outbreaks have been reported. Bats are considered the natural reservoir of the virus.

2) Practicing Good Hygiene: Follow proper hand hygiene practices, such as regular handwashing with soap and water. Avoid touching your face, especially after handling animals or contacting potentially contaminated surfaces.

3) Safe Food Practices: Practice safe food handling and preparation. Cook meat and fruits thoroughly before consumption. Avoid consuming fruits that have fallen from trees, as they may have been contaminated by bats.

4) Personal Protective Equipment: Use appropriate personal protective equipment (PPE) when handling potentially infected animals or specimens, including gloves, masks, gowns, and eye protection.

5) Quarantine Measures: Isolate and quarantine suspected or confirmed NiV

cases to prevent the further spread of the virus. This includes restricting movement and implementing infection control measures in healthcare settings.

6) Health Education and Awareness: Promote public awareness about NiV, its transmission, and preventive measures through educational campaigns. This helps individuals and communities understand the risks and take necessary precautions.

It is essential for healthcare professionals, veterinarians, and individuals working near animals or in high-risk areas to be aware of preventive measures and follow strict infection control protocols.

Vaccine: Vaccine development for the Nipah virus is making significant strides, employing various strategies with promising results in animal models. A notable approach involves a subunit vaccine based on the G glycoprotein (sG) of both Nipah and Hendra viruses, demonstrating cross-protective immune responses. Equivac, a successful horse vaccine against Hendra virus in Australia, utilizes this sG-based technology [36].

Another encouraging avenue is the use of virus vector-based recombinant vaccines, where genetically modified viruses express either the F or G glycoproteins of Nipah virus. This approach has shown effectiveness in providing complete protection against oronasal Nipah virus challenges in animal models after a single dose [37] [38].

Additionally, a virus-like particle vaccine, derived from mammalian cells, has been developed. These non-infectious particles mimic the Nipah virus structure and have demonstrated efficacy in protecting against Nipah virus infections in animal models. While further research and clinical trials are necessary to evaluate safety and efficacy in humans, these vaccine strategies offer promising prospects for preventing Nipah virus infection and controlling outbreaks in the future.

The Nipah virus vaccine is currently undergoing trials in various countries. Unfortunately, in our country Bangladesh, no vaccine is yet available, but efforts are underway to expedite the trial process to ensure the safety and efficacy of the vaccine.

WHO Advice: In the relentless battle against the Nipah virus, where the absence of a vaccine or licensed treatment casts a shadow, our primary arsenal lies not in pharmaceutical interventions, but in the formidable power of awareness and education. The key to reducing and preventing Nipah virus infection in the absence of medical breakthroughs lies in a proactive approach centered on raising awareness of risk factors and equipping individuals with the knowledge to mitigate exposure**.** In the absence of a pharmaceutical shield, our defense hinges on empowering communities through education about practical measures that can effectively curtail the spread of the Nipah virus. Vigilance becomes our vaccine, and knowledge our treatment. When confronted with the stark reality of a Nipah virus infection, the battleground shifts to case management. Here, the emphasis must be on the unwavering delivery of intensive supportive care

measures. In the face of severe respiratory and neurologic complications, our approach must be resolute—providing a lifeline through meticulous and dedicated supportive care. In the absence of a pharmaceutical panacea, our strength lies in the collective determination to educate, inform, and support. Navigating the challenges of Nipah virus requires a united front where awareness is our shield and education our sword, reinforcing the conviction that, even in the absence of a conventional cure, knowledge can be a formidable weapon against the unseen adversary.

8. Conclusion

The emergence of the Nipah virus presents a formidable challenge to public health, characterized by severe clinical manifestations and posing a significant threat through both outbreaks and sporadic cases. Timely detection, surveillance, and heightened awareness among healthcare providers and the general population are critical for early identification and effective management. Continued research efforts are imperative to unravel the complexities of the virus, develop diagnostic tools, and explore potential treatments. International collaboration and information sharing are indispensable for a unified global response, while strengthening public health infrastructure and implementing proactive measures, including vaccination strategies, are crucial elements of a comprehensive approach to mitigate risks. As we navigate the complexities of emerging infectious diseases, a sustained commitment to preparedness, research, and collaborative action remains paramount for safeguarding global health and averting future crises.

Authors' Contributions

For the review article, Dr. Munama Magdum is responsible for study concept and design, acquisition of data, contributions to administrative, technical, and material support, as well as the review of relevant literature. The remaining authors primarily contribute to the critical revision of the manuscript under the guidance of Dr. Munama Magdum.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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