

# Development of Preventive Measures and Treatment Strategies Against Nipah Virus is a Timely Need: Bangladeshi Perspective

Clinical Pathology  
Volume 16: 1–4  
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DOI: 10.1177/2632010X231183314



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**ABSTRACT:** Viral epidemics of variable frequency and severity have wreaked havoc and panic across the world. The Nipah virus (NiV), which has been linked to multiple outbreaks, mostly in South and Southeast Asia, is regarded as one of the deadliest in the world. In Bangladesh, seasonal outbreaks of encephalitis caused by the NiV have occurred annually since 2003. In particular, NiV has numerous characteristics that highlight its potential as a pandemic danger, such as its human-to-human transmission capability and its propensity to infect humans directly from natural reservoirs and/or from other animals. Numerous types of research investigate the pathophysiology and viral mechanisms of disease progression. The NiV and its disease have been studied thoroughly but attempts to implement preventive techniques have met cultural and social obstacles. This review highlights the NiV outbreaks, and its present status, the preventative and control measures implemented, the potential causes of the outbreaks in Bangladesh, and the precautions that must be taken by both government and nongovernment entities to contain the outbreaks and assure a future with fewer or no occurrences.

**KEYWORDS:** Nipah virus, Bangladesh, infectious disease, encephalitis

**RECEIVED:** March 1, 2023. **ACCEPTED:** June 2, 2023.

**TYPE:** Commentary

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Introduction

The single-stranded RNA virus known as the Nipah virus (NiV) is a member of the *Paramyxoviridae* family. The enveloped RNA virus has a negative sense and is a member of the *Paramyxovirinae* subfamily and *Henipavirus* genus. The WHO priority pathogen, which caused multiple outbreaks with a high mortality rate of 40% to 75% in and around South and Southeast Asia (specially Singapore, Bangladesh, India, Cambodia, and the Philippines), was discovered for the first time in Malaysia in 1998 and persisted there until April 1999.<sup>1</sup> During this time, 105 people died as a result of the disease, and 1.1 million pigs were culled.<sup>2</sup> The virus was named Nipah virus (NiV) after the Malaysian hamlet of Sungai Nipah, where pigs infected humans with NiV. The novel virus was originally discovered by Malaysian researchers in the cerebral fluid of a patient in Nipah Township, Negeri Sembilan State, in March 1999.<sup>3</sup> Pigs are most likely the amplifying host, while *Pteropus* fruit-bat is the reservoir host of NiV. The Nipah virus can be spread directly from animals like bats or pigs to humans, contaminated food, or from humans to humans. NiV was originally discovered in April or May of 2001 in Bangladesh, and it was found that bat saliva and excreta were to blame for the infection, which was brought on by consuming raw date palm sap.<sup>2</sup> There have been 330 confirmed instances of the illness

since then. Two hundred thirty-one of the afflicted individuals passed away, representing a relatively high death rate of 71%. A minimum of 139 people became sick by ingesting date juice from bats, and 46 more were exposed by another human carrier.<sup>4</sup> From the neighboring country of India, there were 3 NiV outbreaks noted; in Shiliguri (2001), Nadia (2007), and Kerala (2018). In Shiliguri, 66 instances totaling 45 deaths (about 75%) were reported. Out of 19, 17 victims in Kerala, India, passed away. Nine deaths out of 17 cases were reported during the 2014 NiV outbreak in the Philippines.<sup>5</sup>

## NiV—General Information

The NiV has pleomorphic, spherical, or thread-like encapsulated viral particles that are 40 to 1900 nm in size, just like other paramyxoviruses. The genome size varies between strains and ranges from 18246 to 18252, and each surface projection has an average length of about 17 nm. The Bangladesh NiV has a genome that is 18252 nucleotides in length compared to the Malaysia NiV's which 18246 nucleotides. According to African green monkey studies, the Bangladesh NiV (NiV-BD) is more pathogenic because infection with NiV-BD led to higher levels of respiratory tract viral replication and enhanced oral shedding compared to Malaysia NiV (NiV-MY).<sup>6</sup> With 6 structural proteins, the pathogenicity of the NiV proteins V, C,



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and W is encoded by the P gene. During the initial phase of the viral life cycle, G and F proteins are crucial for binding to and fusing with the host cell. The genome of NiV is released and replicated in the cell following attachment to the EphrinB2/B3 receptor. The mRNA is translated into the primary structural proteins following transcription that is mediated by the P and L proteins. The appropriate progression of transcription and replication is controlled by the N protein. The assembly of the virion from DNA and proteins, the viruses' encapsulation, and its release from the host cell involves the M protein and is crucial.<sup>7</sup>

### Transmission, Symptoms, and Diagnostic Strategies of NiV-Disease

Fruit-bats of the species *Pteropus* are natural reservoirs of this virus. They also expel the virus in their semen, saliva, urine, and feces. As a result, NiV transmission to humans primarily takes place in areas where pigs, humans, and bats are in close contact. The bats are native to the tropics and subtropics of Asia, Australian, and some regions of Africa continent, and certain oceanic islands. Several fruit-eating bats have been found positive for NiV-neutralizing antibodies in a surveillance investigations in Cambodia, Madagascar, Ghana and Thailand. These bats spread NiV to pigs and other animals as well as to people. Transmission can take place through close contact with bodily fluids from an infected person or animal, eating fruit tainted with the NiV virus, or encountering evacuation or secretions of infected animals.<sup>8</sup> The virus causes severe illness that may affect both the central nervous system and the respiratory system in people. The NiV virus takes between 4 and 45 days to incubate. Fever, muscle aches, vomiting, respiratory discomfort, headache, behavioral abnormalities, and low levels of awareness, disorientations with uncontrolled walking are the main characteristics of NiV. Septicemia could develop, the kidneys could get damaged, and there could be gastrointestinal bleeding. In severe situations, encephalitis may develop within 24 to 48 hours associated with seizures, which finally results in coma.<sup>1</sup> Diagnostic tests include polymerase chain reaction (PCR), cell culture for virus isolation, serum neutralization, immunofluorescence assay, and enzyme-linked immunosorbent assay (ELISA) and so on.<sup>9</sup>

### NiV- Status in Bangladesh

According to historical records, the first Nipah case was discovered in Bangladesh's Meherpur district in May 2001, while the second outbreak was discovered in Naogaon district in January 2003. In 2004, it was discovered that the disease was spread by the consumption of raw date palm juice contaminated by bats. In Bangladesh, a hospital-based monitoring system was set up in 2006 to find outbreaks of NiV infection. Currently, 8 Government Medical College Hospitals throughout 8 divisions are participating in the Nipah surveillance program. In addition to this surveillance carried out in hospitals, Institute of

Epidemiology Disease Control and Research (IEDCR) also conducts "Event Based Surveillance." Polymerase Chain Reaction (PCR) tests are used to identify virus nucleic acid in blood and throat swab samples. Enzyme-linked immunosorbent assay (ELISA) is used to identify the IgM and IgG antibodies against the Nipah virus in the serum. Between 2001 and 2011, cases were found in 20 districts of Bangladesh. In 32 districts of Bangladesh, instances were discovered up until 2021. Faridpur district had the most cases (71), followed by Rajbari (30), Naogaon (25), and Lalmonirhat district (24). 322 Nipah cases in total, including 229 (71%) death cases, were recorded from 2001 to 2021.<sup>10</sup> Infections seem to be limited to the central and northwest regions of the country, most likely a greater number of people consume date palm sap in these areas.<sup>11</sup> Outbreaks typically occur between November and May (mostly in December-April).<sup>2</sup> Drinking tainted raw date palm juice and coming into contact with Nipah patients were identified as risk factors in Bangladesh. In 46% of cases, human-to-human transmission took place. After 2011, the consumption of 'Tari', a traditional liquor made by fermenting raw date palm juice, was discovered to be another danger factor.<sup>10</sup> A 35-year-old lady died from Nipah-induced encephalitis in Rajshahi, the IEDCR informed reporters at an event on January 11, 2023. Three Nipah virus cases were reported to the IEDCR in the past year, 2 of which resulted in fatalities, one in Naogaon and the other in Faridpur. The virus has so far affected 330 people. Two hundred thirty-one of them perished.<sup>4</sup>

### Current Treatment and Prevention Strategies

Vaccination is the primary means of protection against contracting any form of virus. Since there are no approved vaccines or medications available to treat NiV-infection, patients can only be managed with supportive and preventative care. Maintaining prophylaxis of venous thrombosis, fluid and electrolyte balance, airway patency, mechanical ventilation are fundamental clinical practices. Additionally, broad-spectrum antibiotics are administered to NiV-infected individuals. It is questionable whether the ribavirin given during the epidemic in Malaysia and the acyclovir given in Singapore were effective. Chloroquine showed efficiency in suppressing Nipah virus in cell cultures, however this result could not be verified in animal models. Effective results were observed after administering Favipiravir in hamster.<sup>7</sup> Several vaccine types have been identified as a result of significant study, which included preclinical testing in a range of animals. The use of the vesicular stomatitis virus as a vector vaccine has demonstrated protection in ferrets, African green monkeys, and hamsters. Advanced vaccinations including virus-like particles, DNA vaccines, live and recombinant virus vectors have been developed.<sup>1</sup> Several viral vectors, such as the vesicular stomatitis virus glycoprotein (VSV-G), the canarypox virus, and the rhabdovirus have been the subject of research for the development of experimental vaccines. It has been discovered

that a recombinant measles virus (rMV) vaccine is promising for usage in humans. In a hamster model, recombinant VSV-vectored vaccination was said to exhibit good efficacy.<sup>1</sup>

The NiV can survive for up to 3 days in fruit juices or mango fruit, and at least 7 days in synthetic date palm sap stored at 22°C. The virus has an 18-hour half-life in fruit-bat urine. In addition to vaccines and therapies, various strategies are essential for preventing and controlling human NiV infection.<sup>1</sup> The Centers for Disease Control and Prevention of the United States (CDC) has also suggested ways to avoid getting the virus. These include washing one's hands often with soap, staying away from sick bats or other animals like pigs, staying away from places where bats are known to live, and staying away from the blood or body fluids of anyone who is known to have NiV. One should also avoid drinking raw date juice.<sup>12</sup> Besides, physical barriers that block a bat's access to the date palm tree's sap stream are preferable alternatives. Farms shouldn't be located next to fruit trees that attract bats and should be planned to minimize overcrowding to prevent the quick spread of disease among animals.<sup>6</sup> Avoiding direct contact with virus hosts and their secretions as well as consumption of infected food should be important. It is crucial to wear the proper protective clothing when performing tasks that require proximity to animals, especially during disposal and slaughter procedures. The spread of the NiV through direct human-to-human contact is a crucial preventive approach that can successfully lower the extent of NiV transmission.<sup>7</sup>

Currently, the Bangladeshi government strongly warns against drinking raw date palm sap during outbreak seasons unless it has been protected by wearing bamboo skirts during collecting or by boiling it for 10 minutes. Harvesters dislike boiling the sap because they believe it modifies the flavor and consistency of the beverage, despite the fact that it renders the virus dormant. Because there are no other therapeutic options than supportive care and no vaccination for people or animals, the government has recently concentrated on prevention by promoting public awareness. They make use of newspaper ads, conversations on regional TV and radio, and talk shows. Before and during each season of the Nipah virus, educational programming is broadcast (November-May).<sup>2</sup> The epidemiology of NiV transmission in Bangladesh recommended 2 methods for human disease prevention. Limiting Bangladeshi villagers' exposure to NiV-infected fresh date palm sap is the first step. The second is to stop the virus from spreading through direct human-human interaction.<sup>13</sup>

## Recommendations

Since there is no known cure for the infection and few effective treatments are available, prevention is essential. At the time, the fruits and date sap are full of nutrients and seasonal as well which have enormous health benefits. Therefore, taking measures to safeguard the palm sap from bats would be prudent. However, controlling Nipah is a difficult task. Healthcare and

agricultural workers should prioritize preventing such zoonotic diseases. The government and the nongovernment organizations (NGOs) as well as the health care professionals and bio-engineers can play a key role to raise awareness to the people specially who are mostly prone to be affected, and can contribute to the development of new technological preventive measures. It will be important for researchers, and people at risk to keep understanding about NiV, in addition to the efforts individuals may take to reduce their risk for infection. Methods to reduce the spread of NiV include better detection tools, increased surveillance of animals and people in areas where the virus is known to exist, more study into the ecology of fruit-bats to learn where they live and how they spread the virus, and the evaluation of novel technologies or methods to reduce the spread of the virus within bat populations.

Education, seminars, and workshops are essential for raising community awareness and preventing the spread of disease throughout the year. The teaching/training would be about the protection of the foods from the bats, pigs and other animals who are prone to spread the virus. Any fume or specific chemical can be developed so that the bats or birds would remain out of the range of the fruit or date plants at least during the harvesting seasons specially in the winter. Taking bitten fruits by bats would be avoided, any structure like iron frame can be employed around the date sapping area.

Unfortunately, there are currently no effective methods for curing people infected with NiV in Bangladesh. In the short term, repurposing drugs can help, but so far there has been no record of a patient being cured of NiV infection using this method. A large-scale implementation of the antiviral medications outlined in the previous section would require extensive clinical testing. Ribavirin, m102.4 monoclonal antibody, and favipiravir, all of which were filed to provide life protection after infection,<sup>14</sup> are just a few examples of medications that have been reported to lessen the severity of the condition. However, to yet, no antiviral medication therapy has been documented in Bangladesh. The timely and appropriate availability of necessary drugs is one contributing factor. Patients with infections may need to be closely monitored in intensive care units, although supportive care is the backbone of therapy. To lessen the disease burden, we can only suggest that intensive care units and life support systems be readily available, which is a challenge for low- and middle-income nations like Bangladesh.

As a preventive measure, green house can be developed for the fruits or date sap, although vigorous research is recommended for this type of measures. Besides these, animals like bats and some birds make sound to overcome the obstacles.<sup>15</sup> They produce echolocation which is a sound system that bats make to find the location of insects and their shape and movement.<sup>16</sup> Likewise, there are some bugs like hawkmoth which can produce ultrasonic wave by vibrating their genital organs to get rid of the bat attacks.<sup>17</sup> By producing artificial frequencies of ultrasound which may cause disturbance in bats'

location precision, and they would be distracted easily. Since there is currently no preventative vaccination or antiviral medication that is effective against NiV, it is urgent that appropriate measures be developed to protect millions of people from contracting the fatal virus. Possible key players in this context include the World Health Organization, the United Nations, the World Bank, and other donor organizations.

## Conclusion

The scarcity of effective vaccines and medications is a major reason for concern about the spread of NiV among humans. Due to their highly pathogenic traits and capacity to infect a wide range of mammalian hosts, including people, the discovery of efficient countermeasures against these biothreats has been a key topic of research. We must comprehend their illness manifestation mechanisms to combat future outbreaks. Preventive strategies can be devised and put into action by incorporating a variety of sectors and using a multidisciplinary approach. The best way to manage a NiV infection is through an inter-professional team approach that involves infectious disease experts, clinicians, mid-level practitioners, nursing staff, coordination between institutes, and international collaboration among ecologists, virologists from the medical and veterinary fields, and other health care professionals. In addition, the public needs to be educated on personal hygiene and food hygiene. To respond promptly upon the discovery of any new case, disinfection protocols, proper isolation, infrastructure facilities, quarantine, trained personnel, and protective clothing should be in place. The development of vaccines and antiviral therapies can be achieved through thorough research into NiV pathogenesis and ongoing surveillance of reservoir hosts, animals, and humans.

## Acknowledgement

The authors would like to pay tribute to all the healthcare professionals who are contributing to the development of a successful healthcare strategy and preventive measures against the deadly infectious diseases all over the world.

## Authors' Contributions

TJU conceptualized and wrote the manuscript. SMRD conceptualized, revised the manuscript, and supervised the project.

JMR, SNS and MMH gave scientific advice. All the authors agreed to submit the manuscript in its current form.

## Data Availability

All the data can be available from the corresponding author upon request.

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