

REVIEW

Emerging trends of Nipah virus: A review

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Email: samanderkaushik@gmail.com**Summary**

Since emergence of the Nipah virus (NiV) in 1998 from Malaysia, the NiV virus has reappeared on different occasions causing severe infections in human population associated with high rate of mortality. NiV has been placed along with Hendra virus in genus *Henipavirus* of family *Paramyxoviridae*. Fruit bats (Genus *Pteropus*) are known to be natural host and reservoir of NiV. During the outbreaks from Malaysia and Singapore, the roles of pigs as intermediate host were confirmed. The infection transmitted from bats to pigs and subsequently from pigs to humans. Severe encephalitis was reported in NiV infection often associated with neurological disorders. First NiV outbreak in India occurred in Siliguri district of West Bengal in 2001, where direct transmission of the NiV virus from bats-to-human and human-to-human was reported in contrast to the role of pigs in the Malaysian NiV outbreak. Regular NiV outbreaks have been reported from Bangladesh since 2001 to 2015. The latest outbreak of NiV has been recorded in May, 2018 from Kerala, India which resulted in the death of 17 individuals. Due to lack of vaccines and effective antivirals, Nipah encephalitis poses a great threat to public health. Routine surveillance studies in the infected areas can be useful in detecting early signs of infection and help in containment of these outbreaks.

KEYWORDS

emerging viral infections, infectious disease, Nipah encephalitis, Nipah virus, viral outbreaks

1 | INTRODUCTION

Emerging viral diseases have great impact on community health in the recent years. During past four decades, many new viral out-breaks have been documented in the different regions of the world. These outbreaks were due to some well-known viral agents like Crimean-Congo hemorrhagic fever, Ebola, Lassa fever, Marburg virus, Middle East respiratory syndrome coronavirus, Nipah, Rift Valley fever, and severe acute respiratory syndrome coronavirus.¹ These viral outbreaks are accountable for considerable mortality, morbidity as well as great economic loss across the globe. Even old viruses like influenza are

capable of reemerging and present new threats of the epidemic and pandemic. These viruses follow the different strategies for infecting humans either directly or through adaptation in the reservoir host animals. According to literature, since 1980 only 87 out of 1399 human pathogens have been found to infect humans directly while majority of them initially infect other susceptible animals which further spread the infection to humans.² Nipah virus (NiV) is very notorious zoonotic type of pathogen, which belongs to genus *Henipavirus* of the family *Paramyxoviridae*.³ NiV causes great spectrum of disease from mild to life-threatening encephalitis or fatal respiratory illness in humans and animals.⁴ NiV was reported for the first time from Malaysian population in 1998.³⁻⁶ In March 1999, a team of eminent virologists from the University of the Malaya isolated a virus from sample of a patient from Sungai Nipah (Nipah River Village) and named it as NiV.⁶⁻⁸ Antigenic, serological, and detailed molecular characterization of this

Abbreviations: CDC, Centers for Disease Control and Prevention; ELISA, Enzyme-linked immunosorbent assay; JEV, Japanese encephalitis virus; NiV, Nipah virus.

newly isolated virus showed cross reaction with antibodies to the Hendra virus (HeV), the other member of genus *Henipavirus*. Further sequencing studies revealed that it is a new type of Paramyxovirus and is about 20% different from HeV in nucleotide homology.⁷⁻⁹

2 | NIPAH VIRUS

Nipah virus is an enveloped virus, pleomorphic in shape (40-1900 nm) having single-stranded negative-sense RNA genome.^{3,10} Under electron microscope, NiV has similar morphological structure pattern as that of other members of *Paramyxoviridae*. NiV is placed along with HeV in the genus *Henipavirus* of family *Paramyxoviridae* as NiV showed 68% to 92% and 40% to 67% homology with HeV in protein-coded regions and non-translated regions, respectively.^{3,7-10} Like other Paramyxoviruses, NiV also has six genes which encode for fusion protein (F), glycoprotein (G), matrix protein (M), nucleocapsid (N), phosphoprotein (P), and polymerase protein (L). Phosphoprotein (P) gene encodes various important accessory proteins known as C, V, and W.^{3,11,12} The C protein plays a very important role in regulation of viral RNA synthesis and virulence factor. V and W proteins are crucial for virulence, and these proteins act by inhibiting the activation of an interferon-inducible promoter.^{11,12} Strain variations have been observed between human NiV isolates collected from the outbreaks in Malaysia, India, and Bangladesh. Similarly, NiV virus isolates from bats samples which were collected from different geographical area also displayed genomic variation.¹²⁻¹⁴ NiV is a newly emerging virus, and also high containment facility is required for NiV study; therefore, limited data is available on virus replication, transcription, translation, and other mechanisms. In *Paramyxoviridae* family, NiV are closer to HeV as compared with other family members. Antibodies against NiV also cross-react with HeV but not against other members of family.¹⁵ In contrast to other paramyxoviruses, genomes of NiV and HeV are much longer, ie, 18.2 and 15.5 kb, respectively. The P genes of both viruses are longer than other members of family.^{16,17} Both of these viruses do not show the hemagglutinin and neuraminidase activities which are common features of other paramyxoviruses. And also, both these viruses have broad host range whereas other paramyxoviruses members have narrow host range.^{18,19}

3 | EPIDEMIOLOGY OF NIPAH VIRUS

The epidemiology related to NiV has not been fully understood as Biosafety level-4 (BSL-4) laboratory facility is required for virus research. The *Pteropus* fruit bat, which is also known as the flying fox (order Chiroptera and genus *Pteropus*) considered as the natural animal reservoirs for NiV.^{4,13} There are about 60 different species of these flying fox, which are found in Asia, China, Australia and some part of Africa as well as the Pacific Islands.²⁰ Experimentally, it is yet to be confirmed whether these flying foxes develop sub-clinical disease or not, after NiV infection to them.^{21,22} Sero-surveillance studies for NiV detection in flying foxes samples were conducted in Malaysia, Cambodia, Thailand, and Bangladesh, where 9% to 25% bats were found positive for the NiV.^{13,23-25} The NiV were isolated from some flying fox urine samples collected from Malaysia and Cambodia.^{13,26}

In Malaysian outbreak, flying foxes acted as natural host for NiV, and pigs acted as a mediator host to humans. Pigs had been infected by indirect contact with NiV infected flying foxes in the endemic regions.^{27,28} The outbreaks of NiV in human population have been documented from Malaysia, Singapore, Bangladesh, and India. NiV has also been isolated and identified in flying foxes in Malaysia, Singapore, Bangladesh, India, Cambodia, and Thailand.²⁹ Until June 2018, five countries (Malaysia, Singapore, Bangladesh, India, and Philippines) are affected due to NiV which was responsible for 643 laboratory confirmed patients and at least 380 (59%) human deaths (Table 1).²⁹ In Cambodia and Thailand, NiV were found only in flying foxes and no NiV infected human case was reported.^{13,25} Direct contact with NiV infected pigs and their products were primarily responsible for the outbreak in Malaysia.²⁸ While in case of Bangladesh and Indian NiV outbreaks, epidemiology was comparatively less well defined. NiV infect the human through the flying foxes and without the involvement of pigs while some evidences indicated person-to-person transmission of NiV.^{29,30}

4 | NIPAH VIRUS OUTBREAKS (1998-2018)

4.1 | Malaysia and Singapore

During September 1998, there was an outbreak of a peculiar disease in some pig-farmers near Ipoh city of Perak state of Malaysia. Another similar outbreak was observed in a town of Sikamat of state Negri Sembilan, Malaysia in December 1998 to January 1999.⁴⁻⁶ Third and largest outbreak with same symptom occurred in neighboring area of Bukit Pelandok (Malaysian) in December 1998.²⁶⁻²⁸ Initially, all these outbreaks were considered due to Japanese encephalitis virus (JEV), which was generally prevalent in these area.^{4,29} In response to this, JEV vaccination and various steps for mosquito control were taken to manage these outbreaks but even after that the disease was expanding continuously.²⁹ The epidemiological data showed that causative agent for these outbreaks was different from JEV because majority of patients were adult as compared with children. Previously, JEV immunized persons were also infected with new agent, and during animal surveillance there were sick pigs with severe barking cough and many dying from the same disease.⁴⁻⁸ A large number of infected individuals were adult males and were directly associated with pig farming. Pigs to human transmissions of NiV were observed in these outbreaks. Control steps like culling of pigs, avoid pig contact, and exchange of pig were taken in affected NiV areas and as a result the infection declined.⁷⁻⁹ During these outbreaks in Malaysia, a total of 265 Nipah encephalitis patients were confirmed out of which 105 (39.6%) deaths were reported.²⁹ Although these outbreaks were comparatively small but mortality rates were very high led to the reason of panic in that area.^{28,29} Various steps including ban on pig transport, public education, national surveillance, and pig culling were taken to control NiV outbreak. Pig farming is one of top industries in Malaysia, and more than one million pigs were culled during NiV outbreaks, resulted in an economic loss between \$350 and \$400 million.³⁰ The NiV infection spread to Singapore due to import of infected pigs from infected area of Malaysia. In early March 1999, 11 pig farmers in

TABLE 1 Morbidity and mortality in humans due to NiV infections^a

S. No	Year/Month	Country	Location	No. of cases	No. of deaths	Case fatality rate, %
1	Sep 1998-April 1999	Malaysia	Perak, Selangor, Negeri Sembilan states	265	105	39.6
2	Mar-1999	Singapore	Singapore	11	1	9
3	Jan-Feb 2001	India	Siliguri	66	45	68.2
4	Apr-May 2001	Bangladesh	Meherpur	13	9	69.2
5	Jan 2003	Bangladesh	Naogaon	12	8	66.7
6	Jan-Apr 2004	Bangladesh	Rajbari, Faridpur	67	50	74.6
7	Jan-Mar 2005	Bangladesh	Tangail	12	11	91.7
8	Jan-Apr 2007	Bangladesh	Kushtia, Naogaon, Natore, Pabna, Thakurgaon	18	9	50
9	Apr 2007	India	Nadia	5	5	100
10	Feb-Apr 2008	Bangladesh	Manikganj, Rajbari	11	9	81.8
11	Jan 2009	Bangladesh	Gaibandha, Nilphamari, Rangpur, Rajbari	4	1	25
12	Feb-Mar 2010	Bangladesh	Faridpur, Gopalganj, Kurigram, Rajbari	17	15	88.2
13	Jan-Feb 2011	Bangladesh	Comilla, Dinajpur, Faridpur, Lal Mohirhat, Nilphamari,	44	40	90.9
14	Jan 2012	Bangladesh	Joypurhat	12	10	83.3
15	Jan-Apr 2013	Bangladesh	Gaibandha, Manikganj, Naogaon, Natore, Pabna,	24	21	87.5
16	Jan-Feb 2014	Bangladesh	13 districts	18	9	50
17	Mar-May 2014	Philippines	Philippines	17	9	52.9
18	Jan-Feb 2015	Bangladesh	Faridpur, Magura, Naogaon, Nilphamari, Ponchoghora, Rajbari	9	6	66.7
19	2018 May	India	Kozhikode and Malappuram	18	17	94.4
	Total			643	380	59

^aAdapted from WHO data.²⁹

Singapore were diagnosed NiV positive with one fatality. All those farmers were involved in the import of live pigs from NiV infected part of Malaysia and had close contact history with the infected pigs.^{4,8} Singapore government took immediate and effective actions against the NiV outbreak including culling of pigs, avoiding contact with NiV infected pigs and also banning of import of pigs from Malaysia.^{4-6,29} After these actions, outbreak was contained and last confirmed NiV case from Malaysia or Singapore was reported in May 1999.⁵⁻⁸ These NiV outbreaks were very serious, and true numbers of infections may be uncertain due to large number of asymptomatic patients.²⁶⁻²⁸

4.2 | India

In early 2001, there was an outbreak of infectious febrile illnesses, occurred in and around of Siliguri city of northern part of West Bengal.^{14,29} Initially, outbreak was suspected due to Measles virus, but retrospectively it was found NiV based on serological analyses of the infected persons serum. Eighteen patient samples were sent to National Institute of Virology, Pune, and NiV was detected in five urine samples by RT-PCR, while another nine serum/blood samples were found positive for NiV by IgM and IgG immunological assay.¹⁴ The outbreak was sudden and highly serious with 66 laboratory confirmed patients of NiV encephalitis and at least 43 (68%) fatalities.²⁹ As per patient observation and history, all the cases were adults without any history of pig or other animal exposure and some evidence of nosocomial transmission. No role of pigs in NiV infection transmission was found, and the outbreak spread mainly from person-to-person contact specifically in hospital settings. The second outbreak of NiV was surfaced during April, 2007 at village Belechuapara,

near to Bangladesh border area in Nadia district of the West Bengal. This outbreak was limited to five persons only, but case fatality rate was 100% as all infected persons died within a week of infection.^{30,31}

Third and recent outbreak was reported from Kozhikode district of Kerala in southern part of India on 19 May 2018.³¹⁻³³ This was the first experience of NiV outbreak in southern part of India. The outbreak started with the death of three individuals within a family. One health care worker involved in the treatment of these family members, also succumbed to infection.³³ The cause of infection was thought to be the human intervention of habitat of bats. The samples of bats from *Pteropus* genus were collected from Kozhikode district and tested at National High Security Animal Diseases Laboratory, Bhopal. A total 10 (19.2%) samples out of 52 samples collected were found positive for NiV by RT-PCR. The human-to-human transmission of infection occurred through droplet infection. The two coastal districts (Kozhikode and Malappuram) of Kerala state were affected due to NiV. As per the reports of Directorate of Health Services, Kerala, there were 13 deaths out of 14 confirmed cases in Kozhikode district, and three deaths out of four confirmed cases were reported from Malappuram district.³² As on July 2018, the outbreak was responsible for 18 confirmed cases out of which 17 (94.4%) persons succumbed to the infection.³¹ World Health Organization helped Government of India by providing technical support to control the infection spread. World Health Organization did not recommend any restriction on travel, trade, or entry screening related to NiV outbreak. No new case of infection was reported after 1 June 2018, and as of 30 July 2018 the outbreak was contained in the state of Kerala.³¹ All these three NiV outbreaks were responsible for 89 laboratory confirmed cases including 67 (75.2%) deaths.²⁹⁻³³

4.3 | Bangladesh

The first NiV outbreak was reported in April 2001 from a village in district Meherpur, Bangladesh with 13 confirmed cases and 9 (69.2%) deaths.^{24,30} Since first identification of NiV from Meherpur, many outbreaks of NiV encephalitis have been documented annually from various parts of Bangladesh (Table 1). Repeated NiV outbreaks have been noted from different districts including Faridpur, Naogaon, Natore, Nilphamari, Pabna, and Rajbari.^{29,34-36} Various sporadic cases of infection and NiV encephalitis have been reported from western and north-western parts of Bangladesh almost annually. These NiV outbreaks were associated with high mortality and pose great health threat in Bangladesh due to highly infectious nature of NiV and poor medical care facilities. These outbreaks affect the several households, suggesting limited person-to-person transmission.³⁷ Unlike Malaysia and Singapore NiV outbreak, no clear animal exposure was identified as a possible source for the disease. During the sero-surveillance studies, *Pteropus* bats in Naogaon were found to have antibodies against the NiV.³⁰ A total of 13 Nipah annual outbreaks have been observed from various parts of Bangladesh till 2015, resulting 261 laboratory confirmed cases with 199 (76.2%) deaths.^{24,29,37}

4.4 | Philippines

During 2014, some serious infection was reported in humans and horses from southern part of Philippines and the mortality rates were very high in human. Horse-to-human as well as human-to-human transmission were also noted during this outbreak.³⁸ The flying foxes (*Pteropus* bats) were most likely responsible for the NiV infections to horses and humans. The NiV outbreak in Philippines was responsible for total 17 laboratories confirmed cases with nine (53%) deaths.^{29,38}

4.5 | Risk factors and mechanisms of transmission of Nipah virus

The epidemiological studies of NiV outbreaks in Malaysia, Singapore, Bangladesh, Philippines, and India suggested that a number of factors play a crucial role in NiV transmission to human. Close contact with NiV infected animals, reservoir animals, and consumption of contaminated food are important factors responsible for NiV transmission.^{32,37} NiV infected pigs were observed as main source for human infections (92%) during Malaysia and Singapore outbreaks.³⁹ NiV infection among pigs and humans probably occurred through respiratory route. Control and experimental study also prove oral and respiratory as main routes of NiV transmission.^{40,41} Close and prolong contact with infected tissue of pigs may be another way NiV transmission.⁴²

In case of Bangladesh outbreaks, no clear evidence of transmission through pigs has been found, but consumption of contaminated food by secretions of flying foxes was one of the main sources of NiV infection.^{37,43} NiV has been isolated from urine and respiratory samples of infected humans during the Malaysian outbreaks, suggesting the possibility of human transmission.^{44,45} In a study involving ferrets as animal model, it was reported that Bangladesh strain of NiV exhibit higher oral shedding than Singapore strain; however, its mechanism has not been well elucidated.⁴⁶ Person-to-person transmission was not experimentally proved in Malaysian and Singapore outbreaks, but there are strong

evidences of the person-to-person transmission in Bangladesh and Indian outbreaks.^{36,37}

4.6 | Pathogenesis of Nipah virus infection

The availability of high level containment facility (BSL-4) hampered the research on NiV which is restricted to very few laboratories around the world.⁴⁷ NiV has been isolated in animal model or Vero cell line from cerebrospinal fluid, throat/nasal swabs, and urine samples collected from patients.^{45,48-50} NiV infection can be best studied in pigs as animal model where it causes mild to severe infection in pigs with low (1%-5%) mortality.^{41,48} Experimentally, NiV can infect cats, dogs, ferrets, and hamsters and can be isolated from various tissues of these animals. These limited studies on NiV pointed out that the incubation period was less than 15 days in majorities of cases.^{46,48,49} However, incubation period may be more in some cases which extends up to 4 months or more.^{50,51} After infection, virus causes viraemia and spreads to different locations and organ systems. The virus also enters into CNS through cranial nerves and is recovered from CSF sample. During infection, CNS (>90%) and respiratory (62%) systems are highly affected while renal, cardiac, and splenic systems are least affected.^{52,53} Sometimes, syncytial multinucleated giant endothelial cells are noted in brain and other organ biopsy samples collected from NiV infected patients. Syncytial multinucleated giant endothelial cells are not common in other types of viral encephalitis which differentiate NiV encephalitis from other viral encephalitis.⁵²⁻⁵⁴

4.7 | Clinical symptoms

Clinical symptoms of NiV infection are broad, ranging from the asymptomatic to very severe.³¹ Sero-surveillance in Malaysia and Singapore noted around 17% to 45% cases of silent Nipah infections while no evidences of asymptomatic infection were found during Bangladesh outbreaks.^{4,24,31} During surveillance studies in Malaysia, 27% pig farmer families were asymptomatic.³⁹ NiV infection in humans produces an encephalitic syndrome which is primarily characterized by headache, pyrexia, and other neurological symptoms. Fever was found to be universal symptom followed by headache in 65% to 88% of NiV patients.^{44,52} There were large differences between the consciousness level of NiV infected patients in Malaysian (55%) and Bangladesh (>90%) outbreaks.^{24,34,44} Apart from fever, other symptoms like vomiting, dizziness, brain stem abnormalities, reduced or absent reflexes, and doll's-eye reflexes were also observed frequently during NiV outbreak.³⁴⁻³⁶ The respiratory symptoms are second most common after neurological symptoms in NiV infection. Cough, cold, and dyspnea were most common respiratory symptoms reported, while abdominal pain, diarrhea, gastritis, and constipation were reported in few cases only.³⁹⁻⁴⁴ Respiratory and abnormal chest symptoms were more frequent in Bangladesh than in Malaysian outbreak. Higher rates of chest and respiratory infections in Bangladesh outbreaks than during Malaysian and Singapore outbreaks may be attributed to human-to-human transmission of NiV in the Bangladesh.^{34-36,46}

4.8 | Laboratory diagnosis

Nipah virus can be diagnosed by virus isolation, histopathology, immunohistochemistry, serological, and molecular diagnostic assays. Virus

isolation is gold standard and is very helpful particularly while determining the etiology of a new outbreak.⁵⁵ NiV can be cultured effectively in the Vero cells and produces cytopathic effect within 3 days.⁵⁶ Human CSF, blood, nasal/throat swabs, urine, and biopsy during acute phase are the choice of samples for NiV isolation.^{28,44,45} From animals like pigs and cats, NiV can be isolated from various tissues like lung, spleen, serum, and kidneys.⁴⁸⁻⁵⁰ During convalescent phases of infection, antibodies against NiV can be detected by enzyme-linked immunosorbent assay (ELISA). These immunological tests can be performed without BSL-4 laboratory for NiV and other similar viruses; however, the sensitivity and specificity of these assays are slightly poorer than molecular assays.⁵⁵ Molecular techniques like RT-PCR, real-time RT-PCR, and other molecular assays can be utilized for further identification of NiV.⁵⁵ Nested primer coding for conserved regions of *M*, *N*, and *P* genes were most commonly used during NiV outbreaks of Malaysia and Singapore.^{11,28} These methods are rapid, sensitive, and specific, and RT-PCR and genome sequencing are necessary for genetic and molecular characterization of NiV, especially when new outbreak occurs.⁵⁵

4.9 | Treatment and prophylaxis

Treatment for NiV is supportive care only as no specific antivirals or vaccines are available till date.³¹ Ribavirin and acyclovir have been used to treat NiV infection during past outbreaks.⁵⁷ In Malaysian outbreak, Ribavirin was given orally or intravenously to patients with NiV encephalitis. The mortality rate was reduced up to 36% when the infected patients were treated with ribavirin.⁵⁸ In Singapore outbreak, acyclovir was given to all NiV encephalitis patients and only one death reported due NiV infection, but the role of acyclovir drug is still unclear.^{58,59} In a recent in vivo study, Favipiravir (T-705) antiviral showed promising results when tested on NiV infected golden hamsters.⁶⁰ A study involving use of vaccine against NiV has shown promising results in hamster models.⁶¹ As Nipah outbreaks are often associated with high mortality and have great impact on community health, there is a strong need of specific antiviral agents for early treatment of NiV.⁵⁸⁻⁶⁰

Nipah virus infections can be prevented by avoiding direct contact with infected and host organisms (fruit bats and pigs) or with their secretions and avoiding consumption of contaminated food by saliva or droppings of bats. Fruits or other products from trees that harbor fruit bats should be checked carefully and washed properly before consumption. NiV can spread through respiratory droplets or by contact transmission; therefore, proper precautions should be taken while caring for an infected individual. While working with NiV suspected patients, frequent hand washing, sanitization with 70% ethanol, and avoidance of direct contact with body fluids like urine, saliva, blood etc. should be followed as standard operating procedures. Surveillance for NiV in humans and reservoir animals should be done in affected areas, which helps in detecting early signs of impending NiV outbreak.^{31,37,56}

5 | CONCLUSION

Nipah virus is a highly infectious paramyxoviral agent which is spread by flying foxes in humans and other animals. NiV causes encephalitis

and respiratory infections in humans. NiV are spreading in various parts of world, and it has the potential of causing severe outbreaks. There are no specific antiviral or vaccine are available for NiV, and only supportive treatment can be given to patents. The very first step in controlling of NiV outbreaks and lessen its impact is early detection. Therefore, continuous surveillance of animal reservoirs and community should be done which at high risk of NiV. Better strategies should be developed for effective management of the livestock especially near the habitats of bats. Also, people should be educated through different awareness programs about food and personal hygiene. Effective vaccination strategies must be developed in near future to combat the threat of infectious agents like NiV.

CONFLICT OF INTEREST

None declared.

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