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REVIEW

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Nipah amidst Covid-19 Pandemic, another Re-Emerging Infectious Disease of Pandemic Potential – a Narrative Review

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ABSTRACT

Introduction: *Nipah virus (NiV) was reported for the first time from the Kampung Sungai Nipah village of Malaysia in 1998. Since then, there have been multiple outbreaks, all of them in South- and South-East Asia. According to the World Health Organization (WHO), up to 75% of Nipah infections were proven to be fatal. Nipah virus belongs to the group of Biosafety Level-4 pathogen associated with high case fatality rate (40–75%).*

Methodology: *According to the PRISMA guidelines for 2020, we searched in four medical databases (PubMed, Google Scholar, EMBASE and Scopus) and selected relevant studies from the past twenty years till November 2021.*

Review: *Nipah virus was first detected in Malaysia's Kampung Sungai Nipah in 1998. By May 1999, the Malaysia Ministry of Health in association with the Centers for Disease Control (CDC) reported a total of 258 cases with a case fatality rate of almost 40%.*

Nipah in Kozhikode: *Experts from the Pune Institute and Bhopal's National Institute of High Security Animal Diseases had collected Bat samples from Pazhoor in Chathamangalam gram panchayat (where a 12-year-old died due to Nipah infection on September 5 carried antibodies of the virus). All Indian outbreaks have seen person-to-person transmission. The virus found in Kerala differed from those two variants in terms of genetic structure. It also differed by 1.96% from the Bangladesh variant. The difference*

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with the Malaysian variant was 8.42%. While PCR is the most sensitive technique for diagnosing active NiV infection, NiV-specific IgM ELISA offers a serological option when PCR is not available.

Conclusion: *Understanding the fruit bat ecology, NiV illness seasonality, and the transmission risk of various intermediate species requires a One Health approach. The danger of reintroduction into animal or human populations cannot be handled without a thorough understanding of the wildlife reservoir.*

Keywords: Nipah virus (NiV), re-emerging disease, fruit bats, Kerala, Biosafety Level-4 (BSL-4), PCR.

BACKGROUND

The 21st century witnessed the most pathogenic and contagious virus outbreaks of zoonotic origin, including severe acute respiratory syndrome coronavirus (SARS-CoV), Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV) and NiV. Nipah is considered one of the deadliest viruses worldwide, with the heaviest mortality rates in some instances. It has several characteristics that increase its risk of becoming a global pandemic, including the facts that humans are already susceptible, many strains are capable of limited person-to-person transmission, as an RNA virus it has an exceptionally high rate of mutation, and if a human-adapted strain were to infect communities in South Asia, high population densities and global interconnectedness would rapidly spread the infection. Nipah disease is listed as one of the WHO priority diseases that pose the greatest public health risk due to their epidemic potential. Given the ongoing pandemic with the above-described instances and deaths even today, are we organized for every other pandemic?

INTRODUCTION

An emerging disease is defined as a new infection resulting from the evolution or change of an existing pathogen or parasite, resulting in a change of host range, vector, pathogenicity or strain, or the occurrence of a previously unrecognized infection or disease. A re-emerging disease is considered an already known disease that either shifts its geographical setting or expands its host range, or significantly increases its prevalence. Nipah viral disease is a zoonotic infection and an emerging disease caused by NiV, an RNA virus of the genus *Henipavirus*, family *Paramyxoviridae*. Nipah virus can be transmitted to humans from animals (such as bats or pigs), or contaminated foods, but also directly from human-to-human. Nipah virus infection in humans causes a range of clinical presentations, from asymptomatic infection (subclinical) to acute respiratory infection and fatal encephalitis, and the case fatality rate is estimated at 40% to 75% (1-3).

Fruit bats of the *Pteropodidae* family are the natural host of NiV. The disease was reported for the first time from the Kampung Sungai Nipah village of Malaysia in 1998. Since then, there have been multiple outbreaks — all of them in South- and South-East Asia. Phylogenetic analysis affirmed the circulation of two major clades of NiV as based on currently available complete N and G gene sequences. Nipah virus isolates from Malaysia and Cambodia clustered within NiV-MY clade, while those from Bangladesh and India clustered within NiV-BD clade. Nipah virus can survive for up to three days in some fruit juices or mango fruit and for at least seven days in artificial date palm sap (13% sucrose and 0.21% BSA in water, pH 7.0) kept at 22 °C. The virus has a half-life of 18 h in the urine of fruit bats (4, 5).

Fruit bats (commonly known as flying foxes) in the genus *Pteropus*, family *Pteropodidae*, are main reservoir hosts of both NiV (Figure 1). Nipah virus naturally infects pigs, horses, dogs,

FIGURE 1. Fruit bats in the genus *Pteropus*, family *Pteropodidae*, the main reservoir hosts of NiV

cats, and humans. A high proportion of victims had direct physical contact with pigs (5). Nipah virus fulfills some criteria to be considered a potential agent for bioterrorism. Preventive strategies include interventions to prevent farm animals from acquiring NiV by eating fruit contaminated by bats. Farms should be designed to reduce overcrowding to avoid rapid spread of the disease between animals and should not be near fruit trees that attract bats. Highly pathogenic NiV causes symptomatic infections in pigs and humans (6, 7). There is no cure or vaccine for Nipah yet, and patients are only given supportive medical care. According to the WHO, up to 75% of Nipah infections prove fatal. Nipah virus belongs to the group of Biosafety Level-4 pathogen associated with high case fatality rate (40–75%) (8). Though it causes a low number of infections, disease severity results in a higher death rate (9, 10).

Aims and objectives

1. To identify the factors related to NiV emergence
2. To determine NiV infectious nature and source
3. Methods for NiV identification

METHODOLOGY

According to the PRISMA guidelines for 2020, we searched in four medical databases (PubMed, Google Scholar, EMBASE and Scopus). We selected relevant studies from the past 20 years till November 2021. Two authors independently searched the databases using the following keywords: Nipah virus, re-emerging disease, epidemiology, history, transmission, fruit bats, symptoms. All related articles were searched. Some articles were also retrieved from cross-references from previously published papers. Only articles published in English were selected. We searched around 102 articles. Then the eligible articles were analyzed.

REVIEW

Nipah outbreaks

Nipah virus was first detected in Kampung Sungai Nipah, Malaysia, in 1998. By May 1999, the Malaysia Ministry of Health in association with the Centers for Disease Control (CDC) reported a total of 258 cases with a case fatality rate of almost 40%. In Malaysia, the government ordered mass culling of more than a million pigs in the outbreak areas, resulting in successful control of the epidemic. The World Health Organization declared the outbreak over in May 1999 (1). In 2001, it appeared in Bangladesh, and the same year the first outbreak of the virus was reported in Siliguri, West Bengal, India, with 65 people infected, of which 45 patients died. The source of infection was represented by pigs in Malaysia and presumably bats, associated with several factors such as bat breeding season, increased virus shedding by bats and fruit harvesting season, in India (1, 4, 7, 11).

Nipah virus caused several outbreaks in Asian countries, including the latest one from the Indian state Kerala. In India there was a second outbreak in Nadia district of West Bengal in 2007, while Kerala reported several cases in 2018 and 2019. Nipah virus is not related to the coronavirus behind the current global pandemic and is far more deadly. It killed a 12-year-old boy in Kerala over the weekend, prompting stepped-up efforts to trace his contacts. But how the victim contracted Nipah was still unclear, despite contact tracing and testing available samples since all were negative. Some reports suggested that the boy in Kerala could have possibly contracted Nipah from eating rambutan — a tropical fruit with thick red spines resembling lychee that grew around his home — sales of the fruit plunged in Kerala (6, 12). All Indian outbreaks have seen person-to-person transmission. Montgomery *et al* (2008) conducted a case control study which showed that climbing trees and contact with another NiVE patient were associated with the infection (6, 13, 14).

Nipah in Kozhikode

Experts from Pune Institute and Bhopal's National Institute of High Security Animal Diseases had collected bat samples from Pazhoor in Chathamangalam gram panchayat (where a 12-year-old child who died due to Nipah infection on September 5 carried antibodies of the virus) earlier in 2018, which killed 17 people out of 19, and in 2019, strains of Nipah were found in bats belonging to the *Pteropus* genus. But in 2021, antibodies detected from bat samples belonged to *Rousettus* genus apart from *Pteropus* type. This was confirmed in the tests done at the National Institute of Virology in Pune (Figure 2). Following this, samples taken from 140 close

FIGURE 2. Nipah in Kozhikode: tests identify bats as source of the virus

contacts and pet animals in the area were negative (12, 15, 16). Nipah antibodies were found in *Pteropus* and *Rousettus* types of bats. Both types are fruit bats.

The virus found in Kerala differed from those two variants in terms of genetic structure. It differed 1.96% from the Bangladesh variant. The difference with the Malaysian variant was 8.42%. It was also different from the structure of the virus that had been earlier found in the Northeastern States. According to ICMR, a new variant of NiV (India I) might be prevalent in South India. It proves that early and rigorous tracing with quarantining is an effective strategy to limit clusters. It would help in significantly reducing the time and effort invested into contact tracing in the event of a person is contracting COVID-19 (12, 14, 17, 18).

Some bats have NiV inside. This virus is transmitted to a newborn bat from its mother at the time of birth. Bats do not beget many progenies. A female bat gives birth to only one offspring a year. Virus-borne bats living in a particular habitat may go to other places owing to the destruction (10, 11). In 2018, the animal source of the virus was not established (2, 19, 20).

Jonathan H. Epstein, Simon J. Anthony, *et al* (2020) sampled 2,789 bats in Faridpur and microchipped 2,345 bats in order to analyse data on host ecology, molecular epidemiology, serological dynamics, and viral genetics to characterize spatiotemporal patterns of NiV dynamics in its wildlife reservoir, *Pteropus medius* bats, in Bangladesh. Model results indicated that local transmission dynamics was modulated by density-dependent transmission, acquired immunity that is lost over time, and recrudescence (7, 15); their data suggested that discrete multiannual local epizootics in bat populations contributed to the sporadic nature of NiV outbreaks in South Asia. At the same time, the broad spatial and temporal extent of NiV transmission, including the recent outbreak in Kerala, India, highlights not only the continued risk of spill over to humans wherever they may interact with pteropid bats but also the importance of limiting opportunities for spill over throughout *Pteropus* range (15, 19, 20).

Yadav PD *et al* (2018) retrieved NiV sequences from samples of four people and three fruit bats (*Pteropus medius*) from a 2018 outbreak in Kerala, India. Phylogenetic analysis demonstrated that NiV from humans was 96.15% like a Bangladesh strain but 99.7%–100% like the virus from *Pteropus* spp., indicating bats as source of the outbreak (18).

Wang L *et al* (2001) performed a phylogenetic analysis which affirmed the circulation of two major clades of NiV as based on currently available complete N and G gene sequences. Nipah virus isolates from Malaysia and Cambodia clustered together in NiV-MY clade, whereas isolates from Bangladesh and India clustered within NiV-BD clade (11, 21). Nipah virus isolates from Thailand harbored mixed population of sequences.

Pathogenesis

The genome of NiV encodes six structural proteins: nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G), and large protein (L) or RNA polymerase. The virus infects its host by entering through the oro-nasal pathway. The site of early replication is uncertain, since human tissues have only been investigated from the latter stages of the illness. However, high antigen concentrations in lymphoid and pulmonary organs suggest that these tissues are likely sites of early replication. NiV glycoprotein G interacts to the receptor complex Ephrin-B2 (alternative receptor Ephrin-B3), which is highly expressed on the endothelium and smooth muscle cells in the brain, lungs, placenta, and prostate as well as blood arteries in other organs (Figure 3). The pathognomonic aspects of this illness are explained by the receptor distribution. Ephrin B2 is extensively conserved across animal species, with receptor similarities between pigs and bats approaching 96%. This explains why NiV has such a broad host range (22, 23).

Clinical features

In humans, the virus is responsible for causing rapidly progressing severe illness, which might be characterized by severe respiratory illness and/or deadly encephalitis (11, 24). Features of

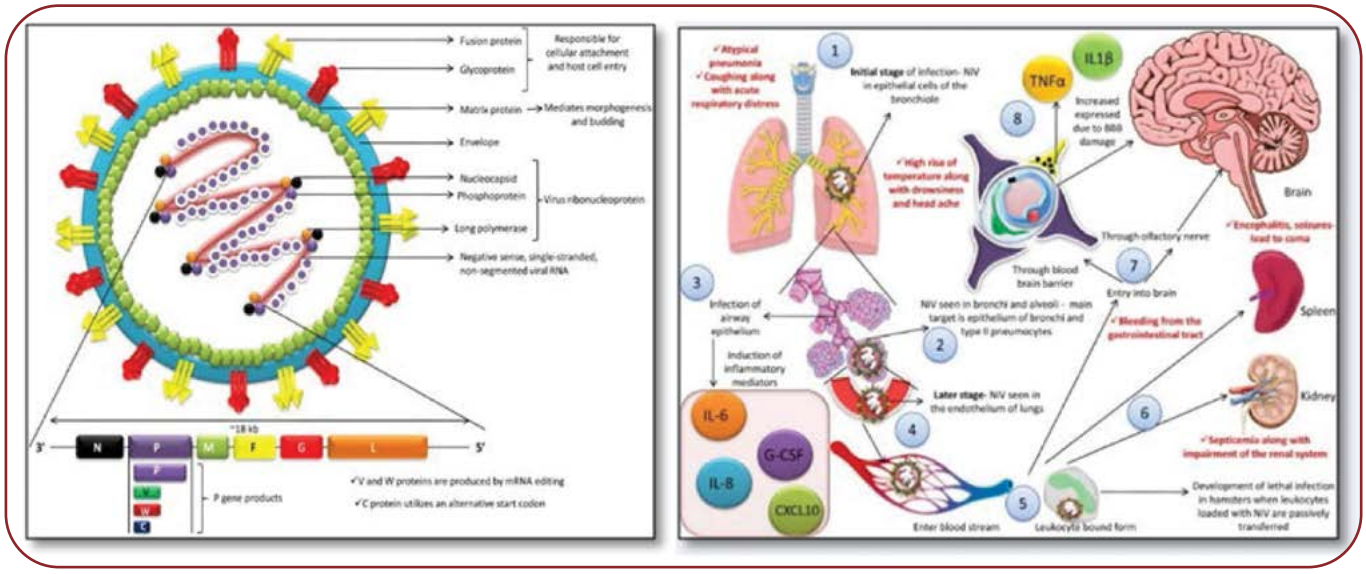

FIGURE 3. Virus structure and pathogenesis

encephalitis develop within a week, with the most common symptoms including altered mental status, areflexia, hypotonia, segmental myoclonus, gaze palsy and limb weakness. Patients deteriorate rapidly and coma and death follow within a few days. Although the condition of people with Nipah can worsen rapidly, symptoms can act as a warning sign for health workers to isolate them in order to avoid contagion (24-26).

In 2008, Hossain *et al* conducted a study in Bangladesh, which showed that all age groups were affected, more severely those under 12, with 62% of the affected persons being males. Fever altered mental status, headache, cough, respiratory difficulty, vomiting, and convulsions were the most common signs and symptoms. Among patients with NiV infection who had well-defined exposure to another patient infected with NiV, the median incubation period was nine days (range, 6–11 days) (22, 27, 28). Cough or breathing difficulties were common during all the first four outbreaks in Bangladesh, while respiratory symptoms were the most common presentation in both Malaysian and Indian (Siliguri) outbreaks in 2001 (29-31).

In 2016, Sauerhering, Lucie *et al* showed NiV replication in primary airway epithelial cell cultures of the two species, with the severity of respiratory symptoms being much more pronounced in pigs than humans, suggesting species-specific differences of NiV replication in porcine and human airways. The authors revealed that NiV growth substantially differed in primary cells between pigs and humans, with a more rapid spread of infection in human airway epithelia (1, 4, 5, 8). The virus spill over is capable to develop infective stages in a human being when successful transmission enables an animal pathogen (6, 7).

Diagnosis

With samples taken from throat, nasal swabs, cerebrospinal fluid, urine, and blood, NiV is detected using antigen-capture sandwich ELISA technique based on rabbit polyclonal antibody to NiV-G protein DNA vaccine, which is likely to help in the rapid diagnosis of new NiV that cannot be detected by conventional polymerase chain reaction (PCR) methods. While PCR is the most sensitive technique for diagnosing active NiV infection, NiV-specific IgM ELISA offers a serological option when PCR is not available. Other methods include molecular diagnostic tests such as real-time or otherwise reverse transcriptase PCR (RT-PCR) and duplex nested RT-PCR. Real-time PCR has been proved to be 1000 times more sensitive than traditional PCR and is now virtually universally utilised. Test results are confirmed by sequencing the products of DNA amplification. For the detection and discrimination of HeV and NiV isolates, microsphere array (Luminex) technology was created. These microsphere assays successfully differentiated HeV and NiV, with HeV detection sensitivity equivalent to individual qPCR. A SYBR

Green-based assay targeting a different region of the N gene has been also developed (32).

Management

Nipah viruses are classed as Biosafety Level-4 (BSL-4) agents due to the severe pathogenicity associated with Henipavirus. For both clinical and scientific activities, safe specimen handling necessitates basic infrastructure, personal protective equipment and stringent operating protocols. There are no antiviral medicines or human vaccinations available for NiV currently. Patients must be segregated, and strict infection control procedures have to be followed. The mainstay of NiV infection treatment is to keep the airway, breathing, and circulation open. The electrolyte and fluid balance are sustained. Mechanical ventilation is required for patients with severe pneumonia and acute respiratory failure. Ribavirin has showed some signs of lowering mortality, although its effectiveness against NiV illness has yet to be shown (33). Chloroquine was reported to be effective in cell culture, but failed to prevent death in a hamster model in isolation or in combination with Ribavirin (34). Acyclovir was used in Singapore, but whether it was effective was unclear (35).

Another method being investigated is represented by passive immunization using a human monoclonal antibody raised against NiV G-glycoprotein, which has shown significant benefit in studies and the use of Cryo-electron microscopy (36, 37). A phase 1 trial showed that a monoclonal antibody called M.102.4 was able to neutralise the virus. Appropriate steps to estimate and manage this risk include studies to explore the molecular and genetic basis of respiratory transmission of henipaviruses, improved surveillance for human infections, support from high-income countries to reduce the risk of person-to-person transmission of infectious agents in low-income health care settings, and consideration of vaccination in communities at ongoing risk of exposure to the secretions and excretions of *Pteropus* bats (16, 17, 38). Although the treatment is still experimental, Kerala authorities have managed to procure the antibodies to stop the outbreak. More hope comes in the form of two experimental Nipah vaccines. One is HeV-sG, funded by the Coalition for Epidemic Preparedness Innovations (CEPI), that has showed promise in clinical trials, indicating that one dose of the vaccine could start offering protection seven days after vaccination. The second, ChAdOx1 NiV is based on the same vector as ChAdOx1 nCoV-19. In results published in a non-peer reviewed paper this July, the vaccine protects non-human primates against NiV (24, 27, 39). Based on the same immunogen as NiV, the Hendra virus attachment glycoprotein ectodomain, a subunit vaccine formulation for use in people, is now in a phase I clinical trial (36, 37, 40, 41).

CONCLUSION

Education programmes may be beneficial in raising community knowledge of the danger of NiV infection, promoting proper care-seeking behaviour, and maintaining vigilance for case detection by healthcare staff. The latest epidemic in India emphasises the likelihood of possible spillover episodes in locations where risk variables are currently unknown. Understanding the fruit bat ecology, NiV illness seasonality, and the transmission risk of various intermediate species requires a One Health approach. The danger of reintroduction into animal or human populations cannot be handled without a thorough understanding of the wildlife reservoir. ❑

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