Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
www.entomoljournal.com
JEZS 2023; 11(1): 208-213

Received: 22-11-2022
Accepted: 26-12-2022

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Nipah virus and its zoonotic importance: A review

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DOI: https://doi.org/10.22271/j.ento.2023.v11.i1c.9158

Abstract
The Nipah virus (NiV) infection is a newly discovered viral zoonotic illness carried by bats. It was discovered for the first time in Malaysia 20 years ago, and since then, outbreaks have occurred in different regions of South and Southeast Asia. It is known to be a highly contagious virus that spreads through sick people or animals to the general populace. The virus exhibits a variety of clinical and epidemiological characteristics. For diagnosis and surveillance, several serological and molecular diagnostic methods have been established. Every time a new area is impacted, diagnosis and management become more challenging. As a result, illness prevention and public health protection present difficult challenges due to the proportionately growing global population. Improvements in diagnosis and very effective therapeutics/prophylactics are essential for the prevention of these infections. Every time an outbreak occurs, it is crucial that the regions upgrade their medical infrastructure and educational programmes. Long-term ecological effects of human activities, including our current methods of animal husbandry, which are a contributing factor in the emergence of a disease, must be a worry.

Keywords: Nipah virus, fruit bats, date palm sap, zoonotic disease

Introduction
Since humans first domesticated animals 10,000 years ago, zoonotic infectious illnesses have been a major problem for them. Globally, infectious diseases continue to be a major source of mortality and morbidity in which zoonoses make up around 75% of emerging infectious diseases (EIDs). Environmental factors, such as climate change and ecosystem changes, changes in human and animal population densities, socioeconomic and political factors, rising international travel and commercialization, genetic and biological factors, microbial adaptation to macro and microenvironmental changes, as well as changes in host susceptibility to infection all plays a major role in the phenomenon of emerging and reemerging infectious diseases [1].

India is one of the world's top hotspots for diseases, including zoonotic infections, due to its rapidly expanding human population, increasing animal-human contacts, changing environmental conditionsand inadequate sanitation and control in which 70% of the zoonotic infections are caused by wildlife especially bats. Ebola, Marburg, SARS and many other zoonotic virus diseases have all been known to be transmitted by bats [2].

In this perspective, Nipah Virus (NiV), one of the most significant bat-borne viruses recently identified, represents another new emerging zoonosis. Bats may have been forced to migrate from their natural habitats to agricultural areas due to urbanisation, deforestation, and drought that reduced the resources available to bat populations. The presence of an amplified, dense host population aided in the virus's ability to spread to people. The illness was initially believed to be a variation of Japanese encephalitis, but it was eventually recognised as a novel zoonotic disease and given the name Nipah after the village "Sungai Nipah," where it was discovered [3]. It is classified as a zoonotic agent of biosafety level 4 (BSL4). Additionally, the National Institute of Allergy and Asthma (NIAA) and the Centers for Disease Control and Prevention (CDC) recognized as Category C priority pathogen.

Etiology
In 1998, the Nipah virus, a new paramyxovirus belonging to the Paramyxoviridae family and closely linked to the Hendravirus, first appeared in a neighbourhood of Ipoh, the state capital of Perak, in the northwest of Peninsular Malaysia [4]. It was classified for two genotypes: genotype M, which includes viral isolates from Malaysia and Cambodia and genotype B, which includes isolates from Bangladesh and India [5].

The NiV contains filamentous nucleocapsids. Its negative strand RNA genome is nonsegmented and has 18,246 or 18,252 nucleotides [6]. The nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G) and large protein (L) or RNA polymeras are the six major structural proteins that are encoded by the six transcription gene units found in henipaviruses. There are also three predicted non-structural proteins: C, V, and W. While the C protein of NiV and likely HeV is expressed from an alternate open reading frame (ORF) within the phosphoprotein (P) gene in other paramyxoviruses, the V and W proteins are expressed through RNA editing [7]. The hemagglutinin and neuraminidase characteristics that are typically present in numerous Paramyxoviruses are absent in NiV. The NiV G and F proteins are necessary for both generating neutralising antibodies and facilitating viral entrance into the cell. Henipaviruses P gene encodes the P protein in addition to at least three other nonstructural proteins (C, V, and W), but P protein is the sole gene product that is absolutely necessary for genome replication [8].

Historical background

It is thought that the Perak state in northern Malaysia's northwest is where the outbreak brought on by the virus afterwards known as the Nipah virus first appeared. An epidemic of encephalitis among agricultural labourers, especially those who had contact with pigs, served as the first warning sign of the emergence of a new illness. From October 1998 through May 1999, there was a human epidemic [9]. The illness was initially described as a JE virus outbreak. Pigs infected with encephalitis were transported from farm to farm from the north to the south and into Singapore, causing the outbreak to spread throughout Peninsula Malaysia. Due to diseased pigs transported in from Malaysia, Singapore documented the subsequent outbreak in 1999 in workers at slaughterhouses [10]. A total of 265 human cases of Nipah were reported in Malaysia and a further 11 in Singapore. Among infected, nearly 40% (105) died.

Retrospective analyses suggest that the initial transmission from the wildlife reservoir into the pig herd started as early as January 1997. NiV was identified as the etiological cause of the outbreak in 1999. The virus was given the name Nipah because it was initially isolated from an infected person in the Malaysian village of Sungai Nipah [11]. Following that, 8 human cases in Bangladesh between 2001 and 2008, all of which happened between December and May were reported [12, 13]. Pigs served as the intermediate hosts in the outbreak in Malaysia. Fruit bats expressing antibodies to the NiV virus were discovered in Bangladesh outbreak, but no intermediate animal hosts were recognised. A person-to-person transmission of the NiV virus was also detected in Faridpur, Bangladesh in 2004.

Outbreak in India

Between January 31 and February 23, 2001, the Indian town of Siliguri (West Bengal) experienced an acute encephalitis outbreak. 45 fatalities and a total of 66 probable human cases were documented. Retrospective analysis was done on the clinical samples collected during the Siliguri outbreak to look for NiV infection [14]. The NiV infections in Bangladesh had many epidemiologic characteristics with the outbreak in Siliguri.

In 2007, the West Bengal district of Nadia reported a second outbreak. Thirty cases of fever were documented, five of which were fatal, along with acute respiratory distress and/or neurological signs. By using RT-PCR, it was discovered all five fatal cases were NiV positive. Khozikode district, Kerala, saw a terrible incidence in May 2018, with an 89% case fatality rate. One case was reported from Kerala's Ernakulum district a year later but the early detection allowed for an immediate stop to the virus's future spread. In September 2021, a 12 year old male from Kozhikode, Kerala who had acute encephalitis and tested positive for NiV died from the NiV infection [15].

Epidemiology

The epidemiologic differences between cases in Malaysia, Bangladesh and India demonstrate that a variety of factors, including close contact with intermediate zoonotic hosts, indirect contact with infected pteropid bats or exposure to their bodily secretions and person-to-person transmission plays a role in the transmission of the Nipah virus. Direct contact with pigs, particularly through close contact, was the main cause of human Nipah virus infection in Malaysia and Singapore [16]. The deadly Nipah virus has been linked to intensive agricultural methods of production. In Malaysia, production of pigs and mangoes increased between the 1970s and the 1990s. Fruit bats were drawn to the area by mango trees, which were frequently placed close to pig farms. Nearby livestock became infected when bats fed and roosted in the trees, which eventually spread to farm labourers [17].

Reservoir and Host Range

The natural reservoir hosts are the large fruit bats of the genus *Pteropus*, also known as flying foxes, specifically *P. vampyrus* and *P. hypomelanus* [18]. *Pteropus* bats have been studied, including Cambodia, Thailand, India, Bangladesh and Madagascar, antibodies against henipaviruses have been found [19]. NiV infection of pteropid bats in an experiment has shown that infected bats expel the virus and produce anti-NiV antibodies without showing any signs of sickness [20]. Pigs plays an important role as the amplifying host. The expansion of intensively run commercial pig farms in Malaysia with fruit trees on the property produced a situation where bats may contaminate fruit with NiV infected bat saliva and drop it into pig stalls. Due to the dense pig population on the farms, the pigs may consume the fruit, contract infection and effectively spread the virus to other pigs [21]. It also can also infect the humans, pigs, bats, dogs, cats, goats and horses [17].

Transmission

NIV transmission from bats to people

Three distinct routes by which the virus can be transmitted from bats to humans have been discovered by epidemiological studies in Bangladesh. Ingestion of fresh date palm sap is the route that is most widely recognized because they ingest the sap at night from the clay pots which is used for the collection of sap. From December through March especially in west central Bangladesh, date palm sap is extracted. Sap slowly drips into an exposed clay pot overnight from a tap drilled into the tree trunk. Fruit bats commonly visit date palm sap trees and suck the sap while it is being collected, according to research using infrared cameras [22].

Domesticated animals are a second means by which the NiV virus is spread from bats to people in Bangladesh. It has been confirmed that the transmission of the NiV virus to humans occurred through direct contact with pigs or fresh pig products [3]. Animals are fed date palm sap that has been

tainted with bat excretion and secretion thus domesticated animals may get infected and spread it to other animals, including people [12].

Thirdly, certain people may come into direct touch with infected bat fluids. It's frequently stated that consuming fruit that has been bitten by a infected bats can cause human Nipah illness [23].

Person to person transmission

Nearly half of Bangladesh's confirmed Nipah case patients contracted the illness after contracting the virus from another individual [13].

Pathogenesis

NiV may first enter the respiratory or digestive tract, possibly through abrasions or breaks in the skin or mucosal surface, where it may infect nearby dendritic cells. Dendritic cells that are infected go through the lymphatic system to local lymph nodes. There, locally created virus binds to lymphocytes, which then leave the lymph nodes and serve as passive carriers for NiV propagation to vulnerable blood vessel cells in various target organs, with the potential to allow virus to cross the blood brain barrier and induce lethal encephalitis [11].

A crucial part of pathogenesis may be played by NiV binding to lymphocytes, which may shield virions and subsequently enable their more effective transit to various tissues.

In general, the Nipah virus produces a wide range of issues in the afflicted host. Inducing the production of syncytial cells is typically the primary mechanism of dissemination with each host, independent of species. The vascular tissue of the infected host was then quickly colonised by these enormous multinucleated cells [24]. High viral antigen concentrations have been identified in the respiratory tract and lung epithelium, supporting the theory that the Nipah virus primarily affects the respiratory system. Infection can also cause haemorrhages and lesions in the brain and lungs, as well as symptoms of anxiousness like twitching and trembling. The first symptom of infection is the beginning of a fever following an incubation period that may last as little as two days or as long as a month.

Clinical manifestation in animals

Pig and other domestic animal Nipah outbreaks were initially documented in the original Malaysian outbreak in 1999 [17]. Due to the severe respiratory and neurological symptoms connected to the disease in pigs, the terms "porcine respiratory and neurological syndrome" and "porcine respiratory and encephalitis syndrome" (PRES) have been proposed as technical names. Barking pig syndrome (BPS) has been proposed as the popular term for the illness since it differentiates from other respiratory disorders of pigs that have been documented in peninsular Malaysia by the unusually loud barking cough. Nipah virus is believed to be very contagious in pigs, and it is most likely conveyed through mechanical contact with oronasal secretions and virus aerosolization caused by coughing [21].

Based on observations of pigs that were naturally infected in the States of Perak, Negeri Sembilan, and Selangor, it was found that the clinical patterns varied depending on the age of the pigs. It was shown that the neurological syndrome predominated in sows, whereas the respiratory syndrome did so in porkers. Pigs' incubation lasts, on average, 7 to 14 days [25].

Weaners and porkers

Pigs between the ages of four weeks and six months frequently displayed an acute febrile illness (>39.9°C) with respiratory symptoms that ranged from rapid and laboured breathing to a harsh, ineffective cough (loud barking cough). The following neurological symptoms could appear alongside the respiratory symptoms: Muscle spasms and myoclonus; trembling and neurological twitches; an uncoordinated gait when hurried; and generalised pain, particularly in the back. Less than 1% to 5% mortality occur, although the infection rate is close to 100%. A disease's symptoms may be absent, minimal, or severe.

Boars and sows

Boars and sows exhibit identical symptoms, and infection may be accompanied by abrupt mortality or acute fever sickness (> 39.9 °C), with laboured breathing, increased salivation (drooling or frothy), and nasal discharge (serious or mucopurulent or bloody). For sows, early abortion is also possible (first three months). The following neurological symptoms may also exist as tetanus-like spasm and seizures; nystagmus; champing of the mouth; and apparent pharyngeal muscular paralysis, which could account for the tongue hanging out of the mouth, difficulty swallowing and frothy salivation.

Suckling pigs (piglets)

Suckling pigs have been shown to have a disease with a mortality rate of about 40%. Most of the infected pigs showed these symptoms like mouth breathing, muscle tremors and paralysis in the legs and neurological twitching.

In post-mortem findings, lungs of affected pigs were found to have various degrees of consolidation and petechiae to ecchymotic haemorrhages. Red colored, foamy secretions were present in the bronchi and trachea in some cases. Generalized congestion and oedema were visible in the brain and kidneys [26]. A moderate to severe interstitial pneumonia with widespread haemorrhages and syncytial-cell formations in the endothelial cells of the lung's blood arteries was the predominant lesion according to histology. Particularly in the lung, kidney and brain tissue, generalised vasculitis with fibrinoid necrosis, haemorrhages and infiltration of mononuclear cells was seen. [8].

Other species

A distemper-like illness with pyrexia, depression, dyspnea, conjunctivitis and purulent ocular-nasal discharge has been reported in dogs. There were additional reports of severe illness with fatality. Immunohistochemical analysis of 1 dead and 1 dying dog from the outbreak area in Malaysia [17] confirmed NiV infection.

Infected dogs had kidney syncytia development, glomerular and tubular necrosis and pulmonary inflammation. Cats can develop endothelial syncytia and vasculopathy in many different organs. A significant amount of bronchial epithelium is prominently involved in the severe pulmonary inflammation. Experimental cats were given oral and intranasal inoculations, which led to the development of a clinical illness marked by an acute fever course and respiratory problems [26]. Fruit bats don't appear to be seriously ill.

Clinical manifestation in humans

Rapid acute encephalitis brought on by NiV has a significant

death rate. The majority of patients reported their cases within two weeks or less during the Malaysian outbreak, which had an incubation period of four days to two months. Fever, headache, wooziness, vomiting, and diminished levels of consciousness were the main clinical manifestations. Segmental myoclonus, hypertension, tachycardia, areflexia and hypotonia were notable clinical symptoms [24]. Encephalitis particularly when the brainstem was involved, were most likely the immediate cause of death. [27]. From the Malaysian outbreak, it was found that 3.7% of patients with non-encephalitic or asymptomatic infection experienced late-onset encephalitis, compared to 7.5% of patients who had recovered from NiV infection. Fever, headaches, convulsions, and focal neurological symptoms were among the clinical characteristics. Relapsed or late-onset encephalitis patients had a lower mortality rate (18%) than acute Nipah encephalitis patients (40%). Additional neurological events in individuals can lead to ataxia, cognitive decline, dysphasia, pseudobulbar palsy, tetraparesis, nystagmus, epilepsy and even death. Patchy areas of confluent cortical lesions were visible on magnetic resonance imaging (MRI), mostly in the cerebral hemisphere [28].

Numerous pathogenic characteristics have been found, mostly at the central nervous system level. Confirmed NiV patients displayed prominent vasculitis in the arterioles, venules and capillaries of multiple organs, along with endothelial damage that reached cellular lyses [28]. The kidney, lung, and heart are another infected organs. Vasculitis was detected in 62% of patients and fibrinoid necrosis in 59% of cases in the lung. Aspiration pneumonia, pulmonary edoema, and alveolar haemorrhage were frequently observed. In 34% of cases, localised glomerular fibrinoid necrosis in the kidney was observed. Vasculitis was seen in 31% of patients in the heart [29].

Diagnosis

Using a combination of tests, a laboratory diagnosis of a patient with a clinical history of NiV can be made during the acute convalescent phases of the illness. Special measures must be taken in the collection, submission and processing of samples since it is a BSL4 agent [30].

Isolation and Identification of the agent

When detecting the cause of a new outbreak, viral isolation in cell culture from damaged tissue is a crucial diagnostic technique for these viruses [30]. It is possible to isolate it from human CSF, urine, nose and throat swabs. In Vero cells, Nipah viruses thrive and they often have a cytopathic effect in 3 days [31]. A CPE typically manifests after 3 days, although two passages of 5 days are advised before declaring the affort failure. The CPE initially appears as the production of syncytia that may have 20 or more nuclei, following low multiplicity infection of cell monolayers. Syncytia then lift off the substrate, puncturing the monolayer of the cell [32]. Immunostaining of fixed, infected cells, neutralisation with certain antisera, PCR of culture supernatants, electron microscopy and immunoelectron microscopy are all methods used to identify viral isolates.

Immunohistochemistry

One of the most effective tests for detecting NiV has been immunohistochemistry. It can be safely carried out on formalin-fixed tissues and has allowed archival material to be studied retrospective.

Electron microscopy

Even during the initial isolation of the virus, it is possible to quickly analysed important details about the virus structure and antigenic reactivity by using immunoelectron microscopy and negative contrast electron microscopy to observe viruses in the medium of infected cells and virus-antibody interactions. The diagnostic process is complemented by other ultrastructural methods such grid cell culture, identification of replicating viruses and inclusion bodies in thin sections of fixed, embedding cell cultures, as well as infected tissues [32].

Polymerase chain reaction

Another helpful tool for detecting viral nucleic acid is the reverse transcriptase polymerase chain reaction (RT-PCR) or nested PCR [33]. Both primary and nested PCR have employed primers based on the N gene of the Nipah virus. The amplified fragments were analysed using restriction enzymes and sequencing to distinguish between the Hendra and Nipah viruses [23].

Serological Methods

Enzyme-linked immunosorbent assays (ELISA) and neutralisation tests are examples of serological techniques. To detect IgM antibodies for Nipah viruses, both indirect formats for IgG and antibody capture ELISA are used. Because of this, ELISA has the advantage of being able to swiftly identify antigen in a larger variety of laboratory environments; the test is also more helpful than serum neutralisation for making a rapid diagnosis in many patients in a suspected-outbreaks. The ELISA test's sensitivity and specificity, however, are marginally lower than those of serum neutralisation assays [31].

Treatment

The basic strategy for addressing the infection in people is intensive supportive care along with symptomatic management. There are very few antiviral strategies against the nipahviruses that have been explored in animal models and there are no recognised or licenced medicines for treating illness in humans. For viral infections with an unclear aetiology, ribavirin is a well-known first-line therapy [34]. In an animal model using ferrets, experimental results showed promises for the therapeutic application of a neutralising human monoclonal antibody, the m102.4, which targets the receptor binding region of the NiV G glycoproteins. Additionally, the m102.4 was successfully used in Non-Human Primate (NHP) models to assess its resistance to the related Hendra virus [35].

Prevention and control

Immunization

There is no vaccine against Nipah virus. Numerous studies on the creation of vaccinations have been completed successfully. Additionally to cats and ferrets, experiments have been carried out on African green monkeys. A HeV soluble G (HeVsG) glycoprotein subunit-based vaccine has been shown to effectively protect animals exposed to otherwise lethal dosages of NiV or HeV from illness and infection [36]. A unique adjuvant has been used in the formulation of the horse vaccine (Zoetis). In order to initiate an infection, the G glycoprotein on the surface of the henipavirus must bind to receptors on the host cells. Antibodies that target this protein can neutralise the virus. In November 2012, the vaccine was made available for use in

Australia under a minor use permit and is only available for administration by accredited veterinarians. For primary immunisation two doses of vaccine should be administered 3 weeks apart in horses four months of age or above. For continued effect, a booster dose every 6 months is currently recommended by the manufacturer [37].

Reducing the risk of infection in people

The only approach to lessen or prevent infection in people since there is no commercially available vaccine is to increase knowledge of the risk factors and inform people of the steps they may take to lessen exposure to the virus.

The key points of public health education communications should be**:**

Reducing the risk of bat-to-human transmission

The primary goal of prevention measures should be to restrict bat access to date palm sap and other fresh food items. It might be beneficial to use protective coverings (like bamboo sap skirts) to keep bats away from sap collection areas. Fruits should be well cleaned and peeled before eating and freshly harvested date palm juice should be cooked. Fruits showing evidence of bat bites should be thrown away. Also the bat exclusion techniques for minimising NiV outbreaks from infected sap is a proven solution in Bangladesh.

Reducing the risk of animal-to-human transmission

When handling sick animals or their tissues, as well as when slaughtering and culling operations are taking place, gloves and other protective apparel should be worn. People should try to stay as far away from diseased pigs as they can. The prohibition on commercial piggeries in Malaysia having mango and other fruit trees that draw *Pteropus* bats is said to have prevented subsequent epidemics. When building new pig farms in endemic areas, it is important to take the existence of fruit bats into account. Additionally, wherever it is practical, pig feed and pig sheds should be secured from bats.

Reducing the risk of human-to-human transmission

Close unprotected physical contact with Nipah virus-infected people should be avoided. Regular hand washing should be carried out after caring for or visiting sick people.

Controlling infection in health-care settings

Health-care workers caring for patients with suspected or confirmed infection, or handling specimens from them, should implement standard infection precautions at all times. As human-to-human transmission has been reported, in particular in health-care settings, contact and droplet precautions should be used in addition to standard precautions. Airborne precautions may be required in certain circumstances. Samples taken from people and animals with suspected Nipah virus infection should be handled by trained staff working in suitably equipped laboratories. If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals with close supervision of burial or incineration of carcasses may be necessary to reduce the risk of transmission to people. The disease can be prevent from spreading by limiting or banning the transport of animals from contaminated farms to other locations. Establishing an animal health/wildlife surveillance system, using a One Health approach, to detect Nipah cases is crucial in order to provide early warning for veterinary and public health authorities.

Conclusion

The spread of the Nipah virus endangers both human and animal health as well as trade and business. Improvements in healthcare, public awareness campaigns, and a holistic "One Health" approach will all be required for the precautions needed to stop new NiV outbreaks in domestic animal and human populations. A deeper understanding of bat reservoirs and the ecological and social factors that contribute to NiV emergence is required to address the root causes of NiV spillover. In all the areas where it exists, better medical facilities and educational opportunities are crucial. In the long run we have to be concerned about the ecological impact of human activities, including our existing animal husbandry practices, which are contributory factor for the emergence of a disease.

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