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Beyond Zoonosis: A One Health Exploration of the Clinical Spectrum of Nipah Virus

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Abstract

Zoonotic diseases, exemplified by the recent COVID-19 pandemic, have posed significant threats to global public health. Among these, the Nipah virus (NiV) stands out as a lethal pathogen responsible for outbreaks with high morbidity and mortality rates. This comprehensive review explores the clinical spectrum of NiV, focusing on epidemiology, transmission dynamics, clinical manifestations, diagnosis, treatment options, recent advancements in vaccine development, and mitigation strategies.

The epidemiology of NiV is characterized by its zoonotic nature, with fruit bats serving as natural reservoirs and various intermediate hosts facilitating transmission to humans and animals. Distinct outbreaks have occurred in different regions, with variations in transmission patterns and clinical outcomes. Clinical manifestations of NiV infection vary across species. In pigs, it leads to swine respiratory and neurological syndrome, while dogs and cats exhibit respiratory distress and renal dysfunction. In humans, NiV infection often manifests as acute encephalitis with diverse neurological symptoms, including sensory disturbances, myoclonus, and late-onset complications.

Diagnosis relies on a combination of assays, including RT-PCR, virus isolation, and antibody detection. Despite the absence of specific treatments, ribavirin and experimental therapies show promise in reducing mortality. Several NiV vaccine candidates are in development, with some showing efficacy in animal models. Prevention and mitigation strategies include livestock infection control, public awareness campaigns, infection prevention in healthcare settings, biosafety measures, and active surveillance. Climate change and human activities contribute to viral spillover, emphasizing the need for a One Health approach to manage NiV and other emerging infectious diseases.

Keywords: *nipah virus, zoonosis, one health, clinical spectrum, epidemiology, transmission, diagnosis, treatment, vaccine, mitigation strategies*

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Evidence in Context

• Nipah virus is mainly transmitted by fruit bats, with a high risk of severe illness and death. • Humans show severe brain inflammation, while animals exhibit respiratory and neurological symptoms. • Diagnosed through RT-PCR and antibody tests; ribavirin offers some potential, though not definitive. • Ongoing vaccine research showing early success in animal trials. • Prevention involves managing livestock, educating the public, and strict biosafety measures.

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Introduction

Zoonotic illnesses have caused countless epidemics over the years that have killed millions of people. The recent COVID-19 pandemic is excellent evidence of this. Like the coronavirus that causes severe acute respiratory syndrome, the Nipah virus is also fatal and has been responsible for several outbreaks in recent years. Recent years have seen several epidemics and pandemics brought on by the H1N1 virus subtype, coronaviruses that cause the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS), A(H5N1) virus, Asian Highly Pathogenic Avian Influenza (HPAI), Rift Valley Fever (RVF), Lassa fever, Crimean-Congo hemorrhagic fever (CCHF), Marburg, Hendra and Nipah virus (NiV), human immunodeficiency virus (HIV), Ebola and Influenza. High morbidity and mortality rates were a defining feature of these epidemics, which primarily affected underdeveloped and developing nations in Asia, Africa, and South America [1,2]. The increasing prevalence of these infectious diseases and the subsequent spread of those diseases have had a profound impact on economics and public health around the world. The emergence of NiV diseases become a serious threat for mammals. The WHO has declared NiV infection as a research and development priority considering no vaccines or therapies are available for this lethal condition [3,4].

Epidemiology

Hendra virus (HeV) and Nipah virus are two zoonotic members of the genus Henipaviruses, which belong to the family Paramyxoviridae. HeV, first identified in Australia in 1994, caused a severe respiratory outbreak with extensive mortality in horses [5,6]. Several cases of HeV infection in horses were subsequently documented in Australia, characterized by notable human transmission and high mortality rates [6-8]. NiV was first recognized as a human pathogen in Peninsular Malaysia in 1998. The outbreak, linked to severe encephalitic illness, resulted in a high mortality rate among pig farmers and slaughterhouse workers exposed to infected swine fluids [9,10]. Negatively polarized single-stranded RNA is present in the Nipah virus. RNA viruses have a higher likelihood of infecting novel host species because of their incredibly rapid evolution and low generation times [11,12]. NiV is a rare but potentially hazardous virus that is to blame for high fatality rates of between 40 -75% [4].

The initial NiV outbreak in Malaysia-Singapore (1998-1999) was initially mistaken for Japanese encephalitis but was later accurately identified [6,13]. In 2001, another NiV outbreak occurred in separate locations: the Meherpur district of Bangladesh and Siliguri in West Bengal, India [14].

Transmission

Fruit bats, often known as megabats and belonging to the Pteropodidae family, especially those from the Pteropus genus, are the natural hosts of NiV. The fruit bats that transfer the virus most frequently are flying foxes, either directly to susceptible species, such as humans, or indirectly through infected fruits (or sap) or biological bat matrices (such as urine or faeces) [4].

Natural NiV transmission can occur between individuals of the same species (humans and pigs) as well as between individuals of different species (flying bats, pigs, and horses). Bovine species are believed to be susceptible to NiV, while ruminants serve as spillover hosts, with confirmed NiV infections in ovine-caprine animals. Although dogs and cats are both capable of contracting the NiV virus, they do not appear to have any zoonotic potential [15]. Human-to-human transmission is a major source of disease and a possible public health threat.

Differential Characteristics of Outbreaks

In terms of transmission, clinical traits, and death rates, the Indo-Bangladesh outbreaks were significantly distinct from Malaysia's. It was primarily marked by human-to-human and nosocomial transmissions. The illness was more severe and progressed swiftly compared to Malaysia's, with acute respiratory distress syndrome (ARDS), respiratory failure, and multi-organ dysfunction syndrome (MODS), along with neurological symptoms, likely causing higher fatalities [14].

Additionally, the strains (BD vs. MY) were blamed for the disparate transmission rates. According to a study, the BD strain in ferrets caused increased RNA levels and more oral

Secretion viral shedding, which may account for the outbreak in Indo-Bangladesh's increased secondary attack rates and severe infection. Notably, viral shedding persisted throughout the incubation period [16].

Table 1 includes a detailed description.

Year of outbreak	Country	Carrier/ Exposure history	Mode of transmission	Case	Case Fertility rate (%)	Clinical Manifestation
1998 and 1999	Malaysia[33,34]	*Pteropus vampyrus*bats	Pig (Pig – Human transmission)	265 - Pig farmers and abattoir workers	105 (40%)	Headache, Dizziness, Fever, Vomiting, Doll's-Eye Reflex, Hypotonia, Tachycardia, Lowering Of Consciousness, Areflexia (Loss Of All Spinal Reflexes), Hypertension And High Mortality.
March 1999	Singapore[34,35]	Island flying foxes (*Pteropus hypomelanus*)	Pig (Pig – Human transmission)	11 Male (Avg age 44 yrs)	1 (9.5%)	Atypical Pneumonia And Encephalitis, Hallucination, Low Lymphocyte And Platelet Counts, High Levels Of CSF Proteins And Of Aspartate Aminostransferase.
Jan 2001–Feb 2023	Bangladesh[36-38]	Fruit bat, i.e.*Eidolon helvum*	Human to Human (Direct consumption of fruit bat-contaminated date palm)	335	237 (75.9%)	More severe and rapid (ARDS, respiratory failure, MODS)
Mar–Apr 2014	Philippines[39]	Fruit bats (family*Pteropodidae*)	Horse (Human to human transmission)	17	9 (52.9%)	Acute Encephalitis Meningitis
2001& 2007- West Bengal, 2018, 2019-Kerala (Isolated case reported in 2021 & 2023)	India [14,40,41]	Fruit bats	Human to Human transmission (1 Nosocomial)	92	68 (73.9%) Kerala 2018 outbreak most deadly (N = 19, CFR 91%).	Fever with acute respiratory distress ± neurologic symptoms

Clinical Manifestation

Pigs

Pigs with an infection exhibit neurological and respiratory clinical symptoms, with varying degrees of severity according to the age of the infected pig. Pigs under the age of four weeks had a death rate of roughly 40%, but pigs aged one to six months had high fevers and one or more respiratory and neurological symptoms like cough, epistaxis, open mouth breathing, seizures etc. Even so, these pigs experienced high rates of illness and modest (<5%) rates of mortality. Some pigs older than 6 months old died within 24 hours without displaying any clinical symptoms. Early miscarriages are also mentioned. The names proposed for pig NiV infection include "Swine Respiratory and Neurological Syndrome" (also referred to as "Swine Respiratory Syndrome and Encephalitis") and "Barking Pig Syndrome" (BPS), as it is commonly known in Malaysia [17,18].

Dogs and cats

Both cats and dogs exhibit symptoms like increased breathing rate, extended expiratory phase, dyspnea, open-mouth breathing, dehydration, vomiting and jaundice. However, oliguria and polyuria as well as other forms of renal dysfunction are also prevalent in dogs.

Humans

More than 90% of subjects develop symptoms within two weeks of exposure, with the incubation period for humans ranging from 4 days - 2 months [19]. Patients may have fever, headache, lightheadedness, and vomiting before developing acute encephalitis. Numerous individuals have significant symptoms of medulla oblongata dysfunction, including sensory blunting, aberrant pupillary reflexes, vasomotor alterations, seizures, and myoclonus [19]. Meningitis, diffuse encephalitis, and focal involvement of the medulla oblongata are just some instances demonstrating the varied and multifocal characteristics of neurological involvement [2]. Cerebellar symptoms are quite common. The recurrence and delayed onset of encephalitis, occurring months or years after the initial acute phase, are unique features of NiV infection [20]. Other symptoms could be mental disorders like verbal and/or visual memory impairment, attention deficit, personality disorders, and/or depression [21].

Diagnosis

During the acute and convalescent periods of the illness, a patient's laboratory diagnosis can be made using a mix of assays if they have a clinical history of NiV. Samples must be handled quickly and transported at 4°C. During the initial stages of infection, RT-PCR and virus isolation from urine, blood, throat, nasal swabs and cerebrospinal fluid (CSF) are advised [22]. During the convalesion stage, antibody detection using ELISA-IgG and IgM from blood or CSF can be done. A useful radiological indicator of Nipah encephalitis can be found on a brain scan using advanced diffusion weighted (DW) MRI technology [14].

Differential Diagnosis

The following differential diagnoses should be considered in those who have a NiV infection: Measles, rabies, cerebral malaria, scrub typhus, leptospirosis, Japanese encephalitis (JE), dengue encephalitis, herpes encephalitis, and bacterial meningitis.

Treatment

In the Malaysian outbreak, the treatment of choice for treating NiV encephalitis was ribavirin, a broad-spectrum antibiotic, which resulted in a 36% decrease in human mortality. Moreover, ribavirin extended the survival of infected hamsters by five days [23,24]. Administration of chloroquine, either alone or combined with ribavirin, showed no protective benefits against NiV [25].

The molecular concentration of favipiravir (T-705) showed suppression of NiV transcription and replication. Favipiravir was given to the animals in the Syrian hamster model either subcutaneously once daily or orally twice daily for 14 days. African green monkeys were given the monoclonal antibody (m102.4) twice following exposure to NiV, once on 1^{st}, 3^{rd}, or 5^{th} day, and again two days later, and it was found that this prevented the disease condition even after the animals had clinical symptoms. Phase I human studies for the monoclonal antibody m102.4 are now underway [11,26].

Patients can be managed with supportive and preventative care because of the lack of a viable medication to treat NiV. If NiV infection is confirmed, maintaining airway patency, preventing venous thrombosis, and maintaining fluid and electrolyte balance are the fundamental therapeutic practises. In cases of severe respiratory problems, mechanical ventilation is employed. Furthermore, individuals infected with NiV are treated with broad-spectrum antibiotics.

Recent Advancements and vaccines

Clinical research on NiV vaccines is limited, with the efficacy of prospective treatments mainly tested in animal models. Research has been conducted on over ten vaccine types, including those based on viral vectors, recombinant protein subunits, mRNA, and virus-like particles. The soluble recombinant Hendra G-glycoprotein (HeV-sG) subunit vaccine, which additionally induces a cross-immune response against NiV, has thus far drawn the most interest. Equivac, developed by Zoetis, Inc., is the only vaccine officially licensed by the Australian Pesticides and Veterinary Medicines Authority (APVMA) for preventive treatment in horses [25,27].

A continual search is being made for novel vaccines. A multi-strain vaccination created by Soltan et al [28] is formulated on the best-ranked epitopes from certain NiV proteins. However, to demonstrate the practical efficacy of this possible vaccine design, experimental trials are necessary.

Mitigation and Prevention Strategies

NiV outbreaks necessitate expensive international emergency measures. Strategies other than immunization wouldbe more cost-effective and play important roles in the prevention and management of human NiV infection. In areas where animals serve as intermediate hosts, preventing infection in livestock may be a successful technique. Such an attempt has already been shown to be very successful in some nations, such as Malaysia [29,30]. Where contaminated date palm sap is the primary source of NiV, managing the virus becomes significantly more challenging. In such regions, altering human behavior through public awareness campaigns is essential, including advising against the consumption of infected date palm sap and emphasizing the need to thoroughly wash vegetables and fruits before eating.

According to the National Centre for Disease Control (NCDC), infection prevention and control efforts at the hospital and household levels help to contain the NiV illness outbreak [31]. Quarantining medical personnel and those at high risk is crucial, as is active surveillance and contact tracing. Special attention must be paid to biosafety and biosecurity measures in order to stop any unintentional or intentional release of high-risk pathogens, particularly those with the potential to spread zoonotic diseases. Local print and broadcast media, including TV and radio channels, can be used to inform local communities about dangers such as consuming contaminated date palm sap. Standard procedures for attending to someone infected or suspected of NiV include washing hands, disinfecting with 70% ethanol, using protective equipment, and avoiding direct contact with the infected individual's bodily fluids [32].

Periodic surveillance should also be carried out in the NiV belt areas to track down early virus outbreak identification, strain analysis, and tracking of the dynamics of theoutbreak illness. To achieve this, specialized research teams are formed to detect potential human infections and assess the appearance of new species as potential carriers of the virus that may cause human disease [25,27].

Large-scale urbanization, deforestation, and industrialization all contribute to climate change by causing droughts and floods, starvation, lowered immunity, and viral load increases in animals. These viruses are then excreted in bat secretions and spread to animals, fruits and people who come to interact with them. Therefore, it is crucial to employ a "one health" strategy that takes into account the health of people, animals, and the environment to manage this specific illness [27].

Conclusion

The COVID-19 pandemic has taught us that any zoonotic virus, particularly one that can spread from person to person, can be extremely harmful and lead to a global pandemic. NiV seems to have the capability to cause a global pandemic due to many factors, including the availability of a vulnerable human population, several viral strains with the capacity for human-to-human transmission, and the error-prone replicating process of RNA viruses and the unavailability of specific vaccines. Given the extensive global travel and trade connectivity, NiV disease outbreaks in densely populated regions like South Asia have the potential to cause pandemics.

Supporting information

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Ethical Considerations

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Subhanwita Manna: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). **Prakasini Satapathy**: conceptualization, Software (lead); writing – review and editing (equal). **Sowntappan Balasubramanian**: conceptualization, Software (lead); writing – review and editing (equal). **Ajay Gupta:** Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal).

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Declaration of competing interest

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