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Navigating Nipah virus outbreaks: Epidemiology, one health strategies, and pathological insights in India

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Abstract
This review article provides a comprehensive overview of Nipah virus (NiV) outbreaks in India, focusing on epidemiology, strains, the One Health approach, and pathology. NiV outbreaks in India have highlighted the virus's significant public health impact, with fruit bats serving as natural reservoirs. The epidemiology section discusses the patterns of NiV transmission, risk factors for outbreaks, and surveillance strategies employed for early detection. Furthermore, the article delves into the genomic diversity of NiV strains, emphasizing the emergence of distinct strains and their implications for outbreak management. The One Health approach underscores the interconnectedness of human, animal, and environmental health in combating NiV outbreaks, highlighting the importance of interdisciplinary collaboration, surveillance, and risk mitigation strategies. Additionally, the review examines the pathological manifestations of NiV infection, detailing the impact on respiratory and central nervous system tissues. Insights from this review inform future research directions and public health interventions aimed at preventing and controlling NiV outbreaks in India and beyond.

Keywords: Navigating Nipah virus outbreaks, epidemiology, one health strategies, pathological insights

Introduction
Over the past two decades, humanity has grappled with a series of viral outbreaks spanning various frequencies and intensities, reminiscent of historical pandemics that have inflicted profound economic and societal burdens. Throughout the annals of time, diseases like influenza, smallpox, measles, and yellow fever have cast long shadows, exacting heavy tolls on economies and human health.

The dawn of the twenty-first century ushered in a new era marked by the emergence of highly virulent and transmissible viruses, many originating from animals, known as zoonotic diseases. Among these, Nipah virus stands out as one of the most menacing, boasting alarmingly high mortality rates and causing devastating conditions such as encephalitis and acute respiratory distress syndrome.

Nipah virus (NiV) presents a formidable challenge, having recently surfaced in regions including Malaysia, Bangladesh, Singapore, and India, where it has left a trail of illness and death in its wake (Goh *et al* 2000) [16]. This lethal pathogen, classified within the Mononegavirales order alongside notorious counterparts such as Hendra, Ebola, and Marburg viruses (Amarasinghe *et al* 2019) [1], finds its origins in Pteropus fruit bats, which serve as its natural reservoirs (Epstein *et al* 2006) [11], perpetuating its cycle of transmission In the face of this ongoing threat, concerted efforts in surveillance, research, and public health interventions are imperative to mitigate the impact of Nipah virus and other emerging zoonotic diseases. By understanding the ecological dynamics of these viruses and investing in preventive measures such as vaccines and therapeutics, we can strive towards a future where the specter of deadly outbreaks no longer looms over humanity.

Epidemiology
Epidemiological studies reveal the timeline and spread of Nipah virus (NiV) outbreaks, highlighting its emergence and impact on human populations. In 1998, NiV was first identified during an outbreak in Sungai Nipah, Malaysia, where transmission occurred from pigs, serving as intermediate hosts to humans (Banerjee *et al* 2019) [4]. Subsequently, in March 1999, 11

male abattoir workers in Singapore contracted acute NiV infection from imported pig meat. Confusion initially surrounded cases in Malaysia, as they were mistaken for Japanese encephalitis or Hendra-like viral encephalitis; however, in 2000, NiV genome sequencing at the CDC in the USA confirmed its identity. The Malaysian Ministry of Health reported 101 human deaths and culled approximately 900,000 pigs in response (Singh *et al* 2019) [2]. Further outbreaks occurred annually in Bangladesh from 2001, attributed to the consumption of raw date palm sap contaminated with bat saliva and excreta. In India, the first outbreak was recorded in Siliguri, West Bengal, in 2001, primarily through nosocomial transmission, with a subsequent outbreak in Nadia, West Bengal, in 2007 (Singh *et al* 2019) [2]. A notable outbreak in 2018 struck the Kozhikode district of Kerala, India, where the index case reportedly contracted NiV from fruit-eating bats. Despite lacking clinical or statistical evidence, the outbreak saw a high fatality rate, reaching 91% (Arunkumar *et al* 2019) [2]. Various factors contribute to zoonotic virus outbreaks, including human-to-human contact and interactions between animals and humans amid environmental changes (Marty *et al* 2001) [28]. Understanding these dynamics is essential for effective prevention and control strategies.

Factors affecting for outbreaks

Factors affecting outbreaks can be multifaceted, involving ecological, environmental, and anthropogenic influences that disrupt ecosystems and environments. These disruptions, such as climate change, resource depletion, deforestation, alterations in natural landscapes, and increased farming and industrial activities, can contribute significantly to the emergence of zoonotic outbreaks (Soman *et al* 2020) [38]. Understanding the epidemiological background of past outbreaks, like the Nipah virus (NiV) outbreak, including its mode of transmission, preventive and control measures, is crucial for addressing current and future outbreaks. Analyzing these factors can help identify potential causes and inform strategies for outbreak prevention and management.

Causative agent: Nipah Virus

The Nipah Virus (NiV) is classified as an enveloped pleomorphic virus within the Henipavirus genus of the Paramyxoviridae family (Ksiazek *et al* 2011) [24]. Its genome comprises a single-stranded RNA encoding six structural proteins: nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G), and RNA polymerase (L) (Harcourt *et al* 2000) [18]. Among these, the N, P, and L proteins form a ribonucleoprotein complex critical for transcription and viral RNA synthesis. The attachment and entry into host cells are facilitated by the F and G proteins embedded in the viral envelope (Tamin *et al* 2002) [39]. The G protein binds to host cellular Ephrin-B2 and -B3 receptor (Chattu *et al* 2018) [6], initiating attachment, while the F protein mediates viral-cell membrane fusion, allowing entry of the virion. This fusion mechanism, coupled with efficient replication strategies, contributes to the high pathogenicity of NiV (Marsh and Wang 2012) [27]. NiV primarily infects host cells through its glycoproteins, G and F. The G protein attaches to host cell receptors, initiating conformational changes that activate the F protein, leading to membrane fusion and cellular entry. Notably, NiV exhibits severe respiratory symptoms in pigs compared to humans, with rapid spread observed in human airway epithelial cells expressing high levels of the ephrin-B2 receptor (Sauerhering *et al*. 2016) [35]. The virus exhibits resilience in various environments, surviving for up to three days in certain fruit juices or mango fruit, and at least seven days in artificial date palm sap. In the urine of fruit bats, a known reservoir, NiV can persist for up to 18 hours. However, it is susceptible to inactivation through heating at temperatures exceeding 100 °C for more than 15 minutes (de Wit *et al* 2014) [9]. Understanding the unique molecular mechanisms and environmental resilience of NiV is crucial for developing effective prevention and control strategies against outbreaks.

Transmission of Nipah Virus

Several high-risk viral diseases, including Nipah, rabies, and Marburg viruses, find their reservoir hosts in bats without significantly affecting the bat population. Fruit bats, in particular, serve as the natural reservoir for Nipah virus across various regions worldwide (Clayton *et al*., 2016) [9]. The transmission of Nipah virus often occurs through spillover events from bats to other species, including humans, but subsequent human-to-human transmission is limited. This transmission to humans is most common in areas where humans, pigs, and bats coexist closely. Pigs are reared for economic purposes, and fruit-bearing trees are often cultivated in proximity, attracting fruit bats of the Pteropus species, the reservoirs of NiV. Consequently, NiV can spill over to pigs and humans. The transmission of infected pig meat across continents has led to the spread of the virus globally. The convergence of factors such as the proximity of fruiting trees, the presence of fruit bats, pigs, and humans creates an environment conducive to the emergence and spread of deadly zoonotic viruses like Nipah. Investigations in Bangladesh have identified three main transmission pathways for Nipah virus. Consumption of fresh date palm sap is the most common route, with the consumption of tari (fermented date palm juice) posing a potential pathway for viral transmission. Preventing bats' access to date palm sap can help prevent NiV infection associated with tari consumption (Islam *et al*., 2016) [23].

Outbreak of Nipah in India

The inaugural occurrence of Nipah virus outbreak in India unfolded between January and February 2001 within the precincts of Siliguri, a bustling commercial hub nestled in West Bengal. Situated adjacent to Bangladesh, Siliguri's proximity added complexity to the investigative process, compounded by initial laboratory setbacks in pinpointing the causative agent. Subsequent retrospective analyses of patient samples eventually unearthed the presence of the NiV virus (Chadha *et al*., 2006) [5]. This grave outbreak exacted a toll of 45 fatalities out of 66 confirmed cases, tallying a harrowing mortality rate of 68%. Notably, transmission during this episode was predominantly nosocomial, with no reported involvement of animals. A recurrence of NiV turmoil surfaced in the Nadia district of West Bengal in 2007, where the entire cohort of five NiV-positive patients succumbed to the infection within a mere 10-day span, registering a staggering fatality rate of 100% (Kulkarni *et al*., 2013) [25]. The most recent and formidable NiV outbreak besieged the state of Kerala in May 2018, thrusting the region into a state of emergency as 23 NiV-positive cases emerged, characterized by a chilling case-fatality rate of 91% (Arunkumar *et al*., 2019) [2]. The specter of Nipah resurfaced ominously in 2019, casting a shadow over Kerala yet again, as a solitary patient tested positive for NiV in the Ernakulam district, serving as a stark reminder of the persistent threat

posed by this virulent pathogen (Soman *et al*., 2020) [38].

Different Strains of Nipah Virus

Genomic sequencing has unveiled the existence of two distinct strains of Nipah virus: NiV-B and NiV-M. A detailed genetic analysis revealed that NiV-B possesses a genome size of 18,252 nucleotides, six nucleotides longer than NiV-M. Despite sharing a substantial 91.8% similarity in nucleotide homology, NiV-B exhibits a reputation for higher fatality rates. These two strains have been implicated in outbreaks across various geographical regions, with NiV-B being linked to outbreaks in Bangladesh and India, while NiV-M is associated with Malaysian outbreaks (Harcourt *et al*., 2005) [17]. Clinical observations have unveiled notable disparities between NiV-M and NiV-B outbreaks. NiV-B manifests a shorter incubation period compared to NiV-M, with a majority of NiV-B cases exhibiting both respiratory symptoms and lethal encephalitis, whereas NiV-M primarily induces encephalitis with minimal respiratory manifestations (Hossain *et al*., 2005) [22]. Furthermore, NiV-B infections tend to result in higher mortality rates, potentially exacerbated by inadequate regional medical resources. Despite NiV-B's propensity for repeated outbreaks, it is intriguing to note that virtually all therapeutic research, both *in vitro* and *in vivo*, has utilized the NiV-M strain rather than the more prevalent NiV-B strain. Animal models, such as hamsters, ferrets, and African green monkeys, have been utilized extensively to explore infection dynamics and disease patterns induced by both strains. Comparative studies between NiV-M and NiV-B infections in hamsters have highlighted distinct differences, with NiV-M displaying rapid disease progression and cytopathic effects, while NiV-B infections exhibit delayed disease progression, altered immune responses, and viral replication kinetics.

Pathogenesis of Nipah Virus

In the early stages of illness in humans, the detection of NiV can be accomplished within the epithelial cells of the bronchioles. Experimental animal models have revealed the presence of viral antigens in both the bronchi and alveoli, with primary targets being the epithelium of the bronchi and type II pneumocytes (Rockx *et al*., 2011) [33]. The infection of the respiratory tract's epithelium induces the production of inflammatory cytokines, triggering the recruitment of immune cells and culminating in the development of a disease resembling acute respiratory distress syndrome (ARDS) (Rockx *et al*., 2011) [33]. This inflammatory response involves significant mediators such as interleukin (IL)-1α, IL-6, IL-8, granulocyte-colony stimulating factor (G-CSF), and C-X-C motif chemokine 10 (CXCL10) when smaller airway epithelia are infected (Escaffre *et al*., 2013) [12]. Distinct pathways facilitate the entry of the virus into the central nervous system (CNS), either hematogenously through the choroid plexus or blood vessels of the cerebrum, or anterogradely via olfactory nerves (Sharma *et al*., 2020) [36]. The infection of the CNS by the virus disrupts the blood-brain barrier (BBB) and leads to the expression of IL-1β and tumor necrosis factor (TNF)-α, resulting in the manifestation of neurological symptoms (Rockx *et al*., 2011) [33]. In cases of CNS infection in humans, inclusion bodies may be present, accompanied by the appearance of plaques and necrosis in both gray and white matter **(**Escaffre *et al*., 2013) [12]. Notably, in several experimental animal models, the virus can directly infiltrate the CNS through the olfactory nerve. NiV infects the olfactory epithelium of the nasal turbinate in these models, subsequently spreading through the cribiform plate into the olfactory bulb and eventually disseminating throughout the ventral cortex and olfactory tubercle.

Clinical signs and symptoms

Highly pathogenic Nipah virus (NiV) causes symptomatic infections in both pigs and humans. Notably, respiratory symptoms tend to be more severe in pigs compared to humans. In humans, NiV induces severe and rapidly progressing illness, primarily affecting the respiratory system and central nervous system (CNS) (Hossain *et al*., 2008) [21]. The onset of signs and symptoms typically occurs 3–14 days after exposure to NiV. Initially, patients may experience a sharp rise in temperature accompanied by drowsiness and headache. Subsequently, mental confusion and disorientation may ensue, progressing rapidly to coma within 1–2 days. Encephalitis represents a critical complication of NiV infection, with respiratory issues often manifesting during the initial phase, including the development of atypical pneumonia. Some patients may exhibit coughing and acute respiratory distress (Hossain *et al*., 2008; Williamson and Torres-Velez, 2010) [21, 40]. Additional symptoms may include sore throat, vomiting, and muscle aches. In severe cases, patients may develop septicemia, renal impairment, and gastrointestinal bleeding. Within 24-48 hours, encephalitis may manifest with seizures, culminating in coma (Giangaspero, 2013) [15].

Post mortem findings

In cases of Nipah virus infection, both the lungs and meninges are identified as key organs affected. Necropsy findings reveal varying degrees of consolidation in the lungs, often accompanied by hemorrhages. Additionally, froth-filled bronchi and trachea are commonly observed. Congestion and generalized edema are prominent in the kidneys and brain, with both the cortex and surface of the kidneys exhibiting congestion. Generalized congestion and edema are also noted in the meninges (Hossain *et al*., 2008) [21]. In dogs infected with NiV, lung inflammation and necrosis of glomeruli and tubules, accompanied by the formation of syncytia in the kidneys, have been reported. In cats, endothelial syncytia formation and vasculopathy in multiple organs may occur. Experimental NiV infection in various animals, including hamsters, guinea pigs, chick embryos, and African green monkeys, results in the development of lesions in the CNS parenchyma along with vasculopathy.

Diagnosis

Early diagnosis plays a pivotal role in managing Nipah virus (NiV) infection due to its high fatality rate. Various specimens are collected from both infected individuals and animals for diagnostic purposes. Human samples typically include nasal swabs, throat swabs, urine, blood, and cerebrospinal fluid (CSF), while deceased animals' lungs, spleen, and kidneys are utilized for NiV diagnosis and isolation. Diagnostic procedures are conducted in enhanced biosafety level 3 (BSL3+) or BSL4 facilities, and tests encompass molecular and serological assays, immunohistochemistry, histopathology, virus isolation, and neutralization. Key diagnostic tests include molecular assays such as real-time polymerase chain reaction (RT-PCR), which primarily target the N, M, and P genes. Virus isolation and neutralization methods are employed but are restricted to BSL-4 facilities (Mazzola & Kelly-Cirino 2019) [29].

Enzyme-linked immunosorbent assay (ELISA) is commonly utilized for antibody detection, including a monoclonal antibody-based antigen capture ELISA for NiV detection and differentiation from HeV. Recently, ELISA assays utilizing recombinant full-length N protein and truncated G protein have been developed for detecting virus-specific antibodies, particularly in porcine serum samples. The High Security Animal Disease Laboratory (HSADL) in Bhopal has also devised a recombinant N protein-based ELISA for screening porcine serum samples. Additionally, a microsphere assay based on luminex technology has been utilized to detect antibodies against NiV glycoprotein sG in pig and ruminant sera, including those from goats and cattle (Singh *et al*., 2019) [2].

Treatment

Currently, there are no specific antiviral medications or antibodies that have demonstrated effectiveness against Nipah virus (NiV) infection. However, during earlier outbreaks in Malaysia and Singapore, Ribavirin and Acyclovir were utilized. Ribavirin, in particular, showed promise by reducing the death toll by 36% during an open-label trial conducted amidst the Malaysian NiV outbreaks. Furthermore, Favipiravir, a purine analogue known for inhibiting RNA-dependent RNA polymerase, has progressed to clinical trials for diseases such as Ebola and various types of influenza. In animal models, specifically Syrian hamsters, Favipiravir has shown efficacy against NiV (Mishra *et al* 2023) [31]. Despite these advancements, the quest for effective treatments against NiV infection remains ongoing.

Prevention

Awareness and preparedness play crucial roles in preventing zoonotic outbreaks like Nipah virus (NiV). Understanding the bat environment and their potential susceptibility as carriers of NiV is imperative. Sampling and sero-surveillance for NiV antibodies in both humans and bats using ELISA and PCR methods are essential steps in early detection and containment efforts. Additionally, adopting personal protective equipment (PPE) kits, masks, and gloves can mitigate the risk of transmission.

Strict prohibition of the procurement and consumption of raw fruits and products under unhygienic conditions in NiV-prevalent areas is paramount to prevent further spread. Vaccination is integral to preventing NiV infection in humans and livestock, especially in endemic regions (Garbuglia *et al*. 2023) [14]. Extensive preclinical research has identified multiple vaccine candidates, including vectored and subunit vaccines, offering protective immunity (Satterfield *et al*. 2016) [34]. Experimental vaccines utilizing viral vectors such as vesicular stomatitis virus (VSV) have shown promise in ferrets, African green monkeys, and hamsters (Liu *et al*. 2021) [26].

Advanced immunization strategies, including DNA vaccines, virus-like particles, and virus vectors (live and recombinant), have been developed for both HeV and NiV (Hauser *et al*. 2021) [20]. However, challenges persist in vaccine development, as pharmaceutical companies are hesitant to invest in rare diseases like Nipah due to their sporadic occurrence despite their high fatality rates. Addressing these challenges requires collaborative efforts between academia, government agencies, and the private sector to ensure the development and availability of effective vaccines to combat NiV and other emerging infectious diseases.

One Health Approach

The One Health approach is crucial for addressing Nipah virus outbreaks, recognizing the interconnectedness of human, animal, and environmental health. Here's how this approach can be applied:

Interdisciplinary Collaboration: Bringing together experts from human health, veterinary medicine, environmental science, and wildlife biology to understand Nipah virus transmission dynamics (Hassan *et al*., 2019) [19].

Surveillance and Early Detection: Implementing surveillance systems to monitor Nipah virus activity in animal reservoirs and human populations for early detection and intervention (Field *et al*., 2018) [13].

Risk Assessment and Mitigation: Identifying factors contributing to Nipah virus transmission and implementing strategies like promoting biosecurity measures to mitigate risks (Middleton *et al*., 2020) [30].

Public Health Education: Educating communities about Nipah virus transmission, symptoms, and preventive measures to raise awareness and promote behavior change (Chua *et al*., 2002) [7].

Vaccination and Treatment: Developing vaccines for humans and livestock to prevent Nipah virus infections, while ensuring access to medical care and supportive treatments for infected individuals (DeBuysscher *et al*., 2014) [10].

Environmental Management: Considering the role of environmental factors in bat habitats and behavior changes, and implementing sustainable land-use practices and habitat conservation efforts (Islam *et al*., 2016) [23].

By integrating these principles into Nipah virus outbreak response strategies, the One Health approach can enhance preparedness, response, and resilience to future outbreaks, ultimately safeguarding the health and well-being of both humans and animals.

Conclusion and Future directions

In conclusion, Nipah virus (NiV) poses a significant public health threat in Southeast Asia, where fruit bats serve as natural reservoirs. Despite its infrequent occurrence, NiV has high zoonotic potential and an alarming fatality rate. Developing a vaccine is imperative to prevent future outbreaks. Strengthening intersectoral coordination, reviewing treatment protocols, enhancing infection control practices, and ensuring the availability of personal protective equipment and drugs are essential measures for managing suspected cases effectively. Additionally, there is a pressing need to advance diagnostic techniques for emerging zoonotic pathogens, employing an integrated One Health approach for optimal outcomes.

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