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State of the Art: Nipah Virus

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Abstract
The Nipah virus (Nv) is a newly recognised zoonotic virus that has been linked to numerous outbreaks characterised by significant mortality rates, primarily occurring in regions of South and Southeast Asia. Nv is known to cause encephalitis and systemic vasculitis, and in certain cases, it is also associated with respiratory illnesses. Fruit bats serve as the primary reservoir of Nv, which can be spread through zoonotic means either directly or through an intermediary host, such as a pig or horse. Numerous investigations have been conducted to investigate the viral mechanism behind illness progression and its broader pathophysiology. Nevertheless, it is imperative to comprehend the pathophysiology and dynamics of the disease in order to facilitate the development of treatment interventions and vaccinations. Therefore, this review aims to present a thorough and up-to-date analysis of the evolving comprehension of the pathogenesis of Nv.

Keywords: Nipa virus; Epidemiology; Pathogenesis; Case fatality rate; Death count; Outbreaks.

1. Introduction

In recent years, there has been a significant impact on public health due to the emergence of viral diseases. Over the course of the past four decades, numerous viral outbreaks have been recorded in various regions across the globe.The epidemics stemmed from a variety of well-known viral pathogens, such as COVID-19, Ebola, Marburg virus, Lassa fever, Crimean-Congo hemorrhagic fever, Nipah virus, Middle East respiratory syndrome coronavirus, Rift Valley fever virus, severe acute respiratory syndrome coronavirus, and Zika virus.(WHO, 2015; 2023). Viral epidemics have been responsible for significant rates of mortality, morbidity, and substantial economic losses worldwide. Even long-standing viruses such as influenza have the potential to reappear and pose novel risks of epidemics and pandemics. Viruses employ various strategies to infect humans, either by direct transmission or by adapting within reservoir host animals. Based on existing literature, it has been observed that since 1980, a total of 87 out of 1399 known human pathogens have been identified as directly infecting humans. It is worth noting that a significant portion of these pathogens initially infect other susceptible animals, which subsequently serve as a source for transmitting the infection to humans (Woolhouse and Gaunt, 2007).Two decades ago, the global community had recently become aware of the Nipah virus, a novel zoonotic paramyxovirus. In 1999, a virus was discovered in Malaysia during a concurrent disease outbreak affecting both humans and pigs (Chua et al., 2000). The outbreak in Singapore transmitted through domestic pigs, which acted as intermediate hosts. A sum total of 276 cases were reported, with 106 deaths. The outbreak was brought under control by eliminating over 1,000,000 pigs (Chua et al., 2000;Gurley et al., 2020).The Nipah virus

(Nv) is classified as an RNA virus within the Paramyxoviridae family. This virus is categorised as a member of the Henipavirus genus, which encompasses other viruses such as Hendra virus (Hv) and the newly discovered Cedar virus (Cv). Bats serve as the primary host for Nipaviruses (Clayton et al., 2013). Although Cv has not been identified to showpathogenicity towards any animal, both Nv and Hvhave been widely recognised for their propensity to induce fatal neurologic and/or respiratory ailments (Marsh et al., 2012). The Nv virus is included in the World Health Organization's prioritized list of pathogens that are expected to produce outbreaks and require immediate advancement and research attention (WHO, 2015; 2023). The Nipah virus is known for its high pathogenicity in a wide variety of mammals and is considered to have the potential to cause a pandemic. This is due to its ability to be transmitted from animals to humans, as well as from person to person (Luby, 2013). The host of infection, Pteropus bats, are globally distributed. It is probable that future consequences will occur in newly inhabited areas. The occurrence of the latest outbreak in a previously unaffected region of Kerala, India is the most recent instance of such an event (Chatterjee, 2018; Shariff, 2019). The Nipah virus has resulted in a limited number of confirmed human cases, numbering less than 700, over the course of two decades since its initial identification. Furthermore, up until now, instances of outbreaks have been effectively controlled within a small number of transmission chains. The Nipah virus is considered one of the most deadly viruses currently identified.The progress of research on this disease has been impeded by the limited number of cases and challenges associated with diagnosis. The Nv is categorised as a Biological Safety Level 4 (BSL 4) pathogen, and its containment is restricted in numerous countries. There is an urgent need for research in the field of epidemiology, specifically focusing on modes of transmission and potential combating and preventing strategies. To effectively control the disease, it is necessary to adopt a one Health approach that considers the interconnections between humans, domestic and peri-domestic animals, and the natural environment.

2. Epidemiology

The epidemiology of Nv remains incompletely understood due to the necessity of conducting research on the virus in a Biosafety level-4 (BSL-4) laboratory facility. The Pteropus fruit bat, commonly referred to as the flying fox, belongs to the order Chiroptera and the genus Pteropus. It is recognised as a primary animal reservoir for theNv (Chua et al., 2000; Reynes et al., 2005). There are approximately sixty distinct species of flying foxes, which inhabit various regions including Asia, China, Australia, parts of Africa, and the Pacific Islands (Koopman et al., 1992). The confirmation of whether flying foxes develop sub-clinical disease after Nv infection is still pending experimental verification (Williamson et al., 1998; 2000). Serological surveillance studies were conducted in Malaysia, Thailand, Cambodia, and Bangladesh to detect the presence of Nvin flying foxes' samples. The results indicated that a range of 9% to 25% of the bats tested positive for Nv (Reynes et al., 2005;Yob et al., 2001; Hsu et al., 2004; Wacharpluesadee et al., 2005). The Nv was isolated from urine samples obtained from flying foxes in Malaysia and Cambodia (Reynes et al., 2005; Chua et al., 2002). During the outbreak in Malaysia, it was observed that flying foxes served as the natural host for the Nv, while pigs played a role as an intermediary host transmitting the virus to humans. Pigs have been found to contract Nv through indirect interaction with afflicted flying foxes in regions where the virus is prevalent (Chua et al., 1999; Chua, 2003) The occurrences of Nv outbreaks in the humanity have been reported in Malaysia, Singapore, India, and Bangladesh.Nv has been isolated and identified in flying foxes in various countries including Malaysia, Singapore, India, Bangladesh, Cambodia, and Thailand. As of the month of March 2023, five countries, namely Malaysia, Singapore, India, Bangladesh, and the Philippines, have been impacted by the Nv. This virus has resulted in 658 laboratory-confirmed and a minimum of 391 human fatalities, accounting for 59.4% of the total deaths(Joshi et al., 2023; WHO, 2023). In Thailand and Cambodia, Nv has been detected exclusively in flying foxes, with no reported cases of Nv infection in humans (Raynes et al., 2005; Wacharapluesadee et al., 2005). The outbreak in Malaysia was primarily attributed to close contact with pigs infected with Nv and their associated products (Chua, 2003). In the instances of the occurrences of Nv in India and Bangladesh, the practise of epidemiology was relatively poorly defined. The Nv is transmitted to humans primarily through contact with flying foxes, without the need for pigs as intermediaries. However, there have been indications of human-to-human spread of Nv based on available evidence (Joshi et al., 2023;

Kulkarni et al., 2013). The map in Figure displays Pteropus bat prevalence and countries with Nipah virus epidemics.

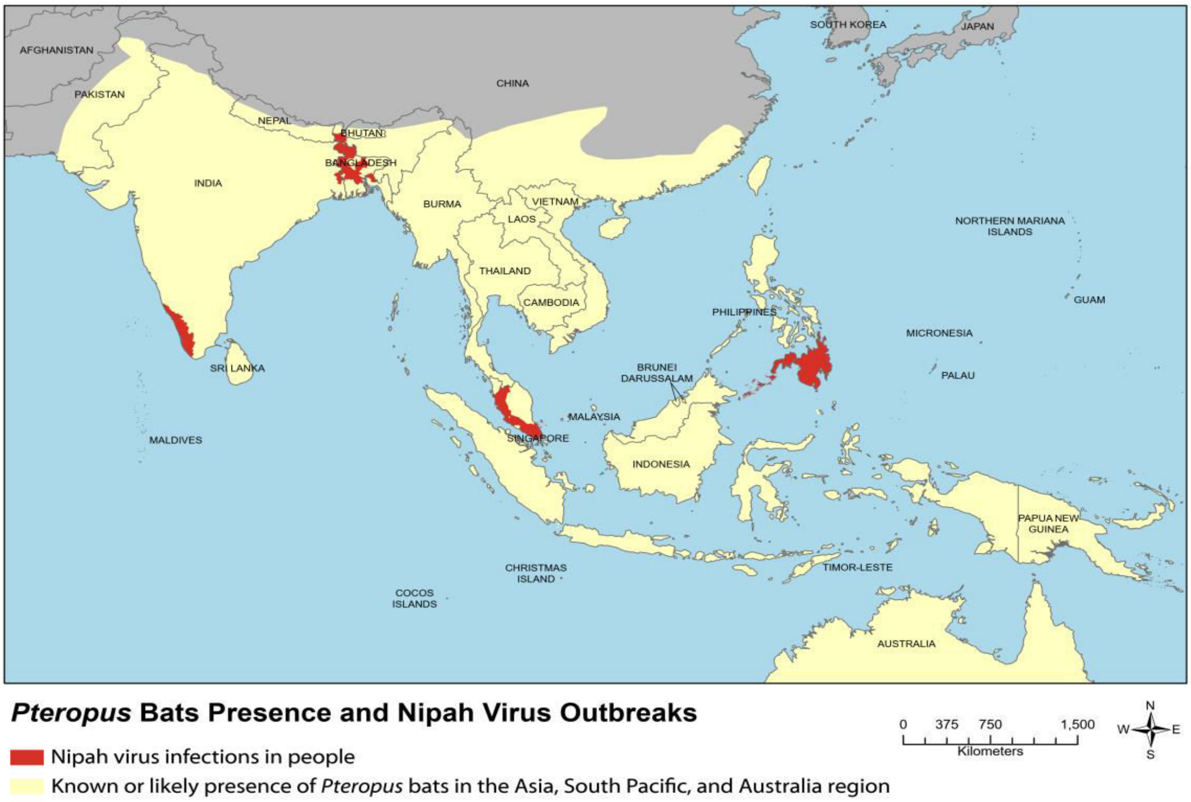
Month/Year	Country and Region	Case count	Death count	Case Fatality rate (%)
September 1998- April 1999	Malaysia (Sembilan States, Selangor, Negeri, Perak)	265	105	39.6
March 1999	Singapore	11	01	9.0
January-February 2001	India (Silliguri)	66	45	68.2
April-May 2001	Bangladesh (Meherpur)	13	09	69.2
January 2003	Bangladesh (Naogaon)	12	08	67.7
January-April 2004	Bangladesh (Faridpur and Rajbari)	67	50	74.6
January- March 2005	Bangladesh (Tangail)	12	11	91.7
January- April 2007	Bangladesh (Thakurgaon,Kushtia, Natore, Pabna and Naogaon)	18	09	50.0
April 2007	India (Nadia)	05	05	100
February-April 2008	Bangladesh (Manikganj and Rajbari)	11	09	81.8
January 2009	Bangladesh (Nilphamari, Rangpur, Rajbari and Gaibandha)	04	01	25.0
February-March 2010	Bangladesh (Faridpur, Gopalganj, Kurigram and Rajbari)	17	15	88.2
January-February 2011	Bangladesh (Lalmohirhat, Comilla, Dinajpur, Faridpur and Nilphamari)	44	40	90.9
January 2012	Bangladesh (Joypurhat)	12	10	83.3
January-April 2013	Bangladesh (Gailbandha, Manikganj, Naogaon, Natore and Pabna)	24	21	87.5
January-February 2014	Bangladesh (13 Districts)	18	09	50.0
March-May 2014	Philippines (Philippines)	17	09	52.9
January-February 2015	Bangladesh (Magura, Nilphamari, Ponchoghor, Naogaon, Rajbari and Faridpur)	09	06	66.7

May 2018	India (Malappuram and Kozhikode)	18	17	94.4
September 2021	India (Kerla)	01	01	100
January-March 2023	Bangladesh (Naogaon, Pabna, Natore, Rajshahi,Narsingdi and Shariatpur Rajbari)	14	10	71.4
Total		658	391	59.4

Source:World Health Organisation (WHO)

2.1malaysia and Singapore

The initial detection of human Nv infection occurred in Malaysia between 1998 and 1999 (Chua, 2003). The term 'Nipah' is derived from the locality of Sungai Nipah, which refers to the village situated along the Nipah River. Several cases characterised by fever, headache, and diminished consciousness have been reported in the state of Perak, Malaysia. This article was published online by Cambridge University Press in September 1998. Initially, four cases were confirmed with positive IgM antibodies against Japanese Encephalitis (JE), prompting the declaration of a JE outbreak. Despite the introduction of multiple control measures, the outbreak has shown a significant increase in intensity. Towards the conclusion of the year, additional clusters were documented within the Port Dickson District, located approximately 300 kilometres to the south (Luby and Gurley, 2012). The isolation of a novel virus, known as Nv, occurred in March 1999 from the cerebrospinal fluid (CSF) of a patient residing in Sungai Nipah village (Chua et al., 1999). In due course, the outbreak resulted in a total of 283 symptomatic cases and 109 fatalities (Chua, 2003). In March 1999, a reported outbreak occurred in Singapore among abattoir workers, resulting in 11 cases and one fatality (Paton et al., 1999). During these outbreaks, it was determined that close contact with pigs or pig excreta posed a significant risk factor (Paton et al., 1999; Parashar et al., 2000). The animals affected exhibited symptoms of mild respiratory illness. In Malaysia, there is a significant concentration of animals in pig farms/slaughterhouses, which is where the outbreak originated and where the potential for animal-to-animal transmission is high. The successful implementation of various control strategies, including the culling of over a million pigs, followed by their disposal through deep burial and decontamination using quick lime, effectively managed the outbreak (Uppal, 2006). Dogs were also observed to be frequently infected (Field et al., 2001), and the occurrence of dogs dying on farms was identified as an additional risk factor (Uppal, 2006). There is currently no substantiated evidence indicating the occurrence of human-to-human transmission in relation to these outbreaks. Ultimately, it was established that Pteropus bats act as the infection reservoir in Malaysia (Rahman et al., 2010), transmitting the infection to amplifying hosts like pigs through the consumption of fruit that had been bitten by bats.



Map in figure illustrating the occurrences of nipa virus outbreaks and the geographical distribution of Pteropus bats andderived from the Nipah virus distribution map provided by the Centres for Disease Control and Prevention.

2.2 India

In the early months of 2001, a wave of infectious viral illnesses broke out in the vicinity of Silliguri city, located in the northern region of West Bengal (Chadha et al., 2006; WHO, 2015). At first, there was a suspicion of an outbreak caused by the Measles virus. However, upon further investigation and subsequent examination of the serum from the infected individuals, it was determined that the outbreak was actually caused by the Nv. A total of 18 patient specimens were submitted to the National Institute of Virology, Pune. Among these samples, Nv was identified in five urine samples using RT-PCR. Additionally, nine serum/blood samples tested positive for Nv through IgM and IgG immunological assays (Chadha et al., 2006). The outbreak exhibited an abrupt onset and was characterised by a significant severity, resulting in 66 laboratory-confirmed cases of Nv encephalitis. Tragically, the outbreak also led to a minimum of 43 deaths, accounting for approximately 68% of the total cases (WHO, 2018). Based on patient testimony and medical history, it was noted that all cases involved adult individuals who did not have any known contact with pigs or other animals. Additionally, there was some evidence suggesting that the spread of the disease occurred within the hospital setting. There was no evidence indicating the involvement of pigs in the transmission of Nv infection. The outbreak primarily occurred through contact between people, particularly within hospital environments. The 2nd outbreak of Nv occurred in April 2007 in Belechuapara village, located near the Bangladesh bordering area in the Nadia district of West Bengal. The outbreak was confined to a total of five individuals. However, it is important to note that the case mortality rate was 100%, as all infected individuals succumbed to the infection within one week (Kulkari et al., 2013; WHO, 2018). A third and new outbreak emerged on May 19, 2018, in the Kozhikode district of Kerala, located in the southern part of India (WHO, 2018; DHS, 2018; Chatterjee, 2018).This marks the initial occurrence of the Nv outbreak in the southern region of India. The outbreak commenced following the unfortunate demise of three people within a single family. A healthcare professional who was involved in the treatment of these family members also tragically passed away from the infection (DHS, 2018). The infection is thought to have resulted from human interference in the natural habitat of bats. Bat samples from the

Pteropus genus were gathered in the Kozhikode district and later analysed at the National High Security Animal Diseases Laboratory in Bhopal. Out of the 52 samples collected, a total of 10 samples (19.2%) were determined to be positive for Nv through RT-PCR analysis. The transmission of infection between individuals was facilitated through the spread of infectious droplets. The Nv outbreak had a significant impact on the coastal districts of Kozhikode and Malappuram in the state of Kerala. According to the reports from the Directorate of Health Services in Kerala, it has been observed that there were a total of 14 confirmed cases in Kozhikode district, out of which 13 resulted in fatalities. Similarly, in Malappuram district, there were four confirmed cases, out of which three individuals unfortunately passed away from the illness (WHO, 2018). As on July 2018, the outbreak resulted in 18 confirmed cases, with 17 individuals (94.4%) unfortunately succumbing to the infection (Kulkarni et al., 2013). The World Health Organisation (WHO) provided valuable technical assistance to the Government of India in order to effectively manage and mitigate the spread of infections. The World Health Organisation has not issued any recommendations regarding travel restrictions, trade limitations, or entry screening measures in relation to the Nv outbreak. A fourth occurrence of Nv has been reported in Kerala on September 2021, resulted in 1 confirmed case, with 1 individual (100%) succumbing to the disease (Joshi et al., 2023). There were no additional reported cases of infection following September, 2021. As of October, 2021, the outbreak in the state of Kerala had been successfully contained.The four Nvoutbreaks collectively resulted in a total of 90 laboratory-confirmed cases, with 68 deaths accounting for 76% of the cases (Joshi et al., 2023; Chadha et al., 2006; DHS, 2018).

2.3 Bangladesh

The epidemiological characteristics of the Nipah virus (Nv) exhibit notable disparities within the context of Bangladesh. Since the year 2001, there have been recurring instances of Nv outbreaks during the wintertime in Bangladesh. These outbreaks predominantly take place in 20 districts (IEDCR, 2018) located in central and north-western regions of the country, which are commonly referred to as the 'Nipah belt'. It is worth noting that a significant number of spill over events transpire within this particular geographic area (Luby and Gurley, 2012). The Pteropus bats have been duly recognised as the reservoir (Yadav et al., 2012). While it has been duly noted that a significant number of patients in Bangladesh have reported instances of interaction with pigs, it is worth highlighting that a specific outbreak has identified close proximity to these porcine creatures as a discernible risk factor (Rahman et al., 2012). Transmission within the geographical confines of Bangladesh can manifest itself through a multitude of pathways. The consumption of unprocessed sap derived from the date palm tree stands as the prevailing mode of transmission for zoonotic infections originating from bats and subsequently affecting the human population (Luby et al., 2006). The occurrence of outbreaks aligns with the temporal period of sap harvesting, which typically spans from the month of December to May. It has been observed that Pteropus bats exhibit a proclivity for frequenting date palm trees, where they engage in the activity of delicately partaking in the sap streams that are being diligently collected. Bats possess the potential to inadvertently introduce urine or faecal matter into the sap collection receptacles (Salah Uddin et al., 2010). It is plausible that domesticated animals could potentially function as a conduit for the transmission of pathogens from bats to humans. Pigs in Bangladesh exhibit a notable seroprevalence against the Nipah virus (Chowdhury et al., 2014), despite their non-involvement in any reported outbreaks within the region. The observed phenomenon can be attributed to the variances in animal husbandry practises between the regions of Bangladesh and Malaysia. In the context of Bangladesh, it is noteworthy that the prevailing practise deviates from the conventional model of large-scale slaughterhouses. Instead, individual proprietors assume ownership of animals in modest collectives, thereby mitigating the likelihood of inter-animal transmission. Seroprevalence studies have revealed that additional members of the animal kingdom, namely cattle and goats, have demonstrated susceptibility to the aforementioned condition (Chowdhury et al., 2014; Chua et al., 2000). The transmission of infectious agents from one individual to another, known as person-to-person spread, holds significant relevance within the context of Bangladesh, as it has been consistently observed as a prominent mode of transmission in all outbreak scenarios. The most substantial instance of interpersonal transmission took place in Faridpur during the year 2004 (Gurley at al., 2007). Nv is effectively transmitted through the mechanism of droplet infection (Homaira et al., 2010), whereby the virus is disseminated via respiratory droplets. It is noteworthy that the genetic material of Nv, specifically its RNA, has been identified in the saliva of afflicted individuals (Harcourt et al., 2005). Additional potential avenues encompass residing beneath a bat roost, wherein the excretion of bat urine may engender contamination of the immediate vicinity. Nevertheless, a conspicuous dearth of empirical substantiation for the aforementioned hypothesis has been ascertained (Hughes et al., 2009). The potential transmission of pathogens through the consumption of fruit that has been bitten by bats has been a subject of suspicion, yet concrete evidence to substantiate this claim has remained elusive thus far. The prevailing modalities of transmission in Bangladesh have been ascertained to be the consumption of date palm sap and interpersonal transmission (Hegde et al., 2016). A cumulative total of 14 annual outbreaks of Nipah virus have been documented in different regions of Bangladesh up until 2023. These outbreaks have led to 275 laboratory confirmed cases, with a mortality rate of 76%, resulting in 209 deaths.

2.4 Philippines

In 2014, there were reports of a significant infection affecting both humans and horses in the southern region of the Philippines. The mortality rates observed in humans were alarmingly high. During the outbreak, transmission between horses and humans, as well as between humans, was also observed (Ching et al., 2015). It is highly probable that the Nv infections in horses and humans were caused by the Pteropus bats, commonly known as flying foxes. The Nv outbreak in the Philippines resulted in a total of 17 confirmed cases in laboratories, with nine deaths, accounting for 53% of the cases (WHO, 2018;Ching et al., 2015).

3. Risk Factors and Mechanisms Of Transmission of Nipah Virus

The epidemiological investigations pertaining to the Nv incidents in Malaysia, Singapore, India, Philippines, and Bangladesh have postulated that a multitude of factors exert a pivotal influence on the transmission of Nv to the human population. Proximity to animals infected with the Nipah virus, animals serving as reservoirs for the virus, and the ingestion of food contaminated with the virus are significant contributing factors to the transmission of Nv(DHS, 2018; Islam et al., 2016).During the outbreaks in Malaysia and Singapore, it was observed that pigs infected with the Nipah virus constituted the primary source of human infections, accounting for a significant majority (92%) of cases (Parashar et al., 2000). The transmission of Nv infection, both in pigs and humans, is believed to have transpired via the respiratory pathway. Both control and experimental studies have provided evidence that the primary modes of Nv transmission are through the oral and respiratory routes (Hooper et al., 2000; Nor et al., 2000). Establishing and maintaining intimate and protracted physical proximity with afflicted porcine tissue could potentially serve as an additional avenue for the transmission of the Nipah Virus (Paton et al., 1999).

Regarding the outbreaks in Bangladesh, it is worth noting that there is currently a lack of conclusive evidence pertaining to the transmission of the virus through pigs. However, it has been observed that the intake of contaminated food, which has come into contact with the fluids of flying foxes, has emerged as a prominent source of Nipah Virus infection (Islam et al., 2016; Luby et al., 2006). The isolation of Nv from urine and respiratory samples of afflicted individuals during the Malaysian outbreaks has provided compelling evidence that human transmission may indeed be a plausible occurrence (Goh et al., 2000; Chua et al., 2000). In a scholarly investigation encompassing the utilisation of ferrets as an animal model, it has been duly noted that the Bangladesh strain of Nv demonstrates a greater propensity for oral shedding in comparison to the Singapore strain. Nevertheless, the precise underlying mechanism responsible for this phenomenon remains inadequately expounded upon (Clayton et al., 2012). The experimental verification of person-to-person transmission remains inconclusive in the outbreaks observed in Malaysia and Singapore. However, compelling evidence has emerged indicating the occurrence of person-to-person transmission in the outbreaks witnessed in Bangladesh and India (Gurley et al., 2007; Islam et al., 2016).

4. Pathogenesis

The limited number of laboratories worldwide equipped with high level containment facilities (BSL-4) has posed a challenge to the research on Nv (Lo and Rota, 2008). The Nv virus has been effectively isolated in animal models and Vero cell lines through the utilisation of several biological resources, including throat/nasal swabs,urine samples and cerebrospinal fluid procured from individuals who have contracted the infection(Chua et al., 2001; Middleton et al., 2002; Wong et al., 2003; Chang et al., 2006). The Nv infection can be effectively studied in pigs as animal model, as it induces a range of infection severities from mild to severe, resulting in a relatively low mortality rate of 1% to 5% (Middleton et al., 2002; Nor et al., 2000). In experimental studies, it has been observed that Nv has the ability to infect a range of animals including cats, dogs, ferrets, and hamsters. Furthermore, the virus has been successfully isolated from various tissues of these animals. The available studies on Nv have indicated that the incubation time was found to be shorter than fifteen days in the majority of cases (Clayton et al., 2012; Middleton et al., 2002; Wong et al., 2003).However, in certain cases, the time of incubation may be longer, extending up to a duration of 4 months or even more (Chang et al., 2006). Following infection, the virus induces viremia, allowing for dissemination to various anatomical sites and organ systems. The virus is also capable of entering the central nervous system (CNS) through cranial nerves and can be detected and isolated from cerebrospinal fluid (CSF) samples. During the course of infection, it has been observed that the central nervous system (CNS) is significantly impacted in over 90% of cases, while the respiratory system is affected in approximately 62% of cases. On the other hand, the renal, cardiac, and splenic systems appear to be less affected by the infection (Wong et al., 2001; Weingartl et al., 2005). Syncytial multi nucleated large endothelial cells have been observed in the brain and other organ biopsy specimens obtained from patients infected with Nv. Syncytial multinucleated giant endothelial cells are a distinguishing feature of Nv encephalitis, setting it apart from other forms of viral encephalitis (Wong et al., 2001; Weingartl et al., 2005; Wong et al., 2002).

5. Clinical Signs and Symptoms

There are variations in the incubation period of Nv observed in different regions. The reported incubation period in Malaysia ranged from four days to two months. The period of incubation in Bangladesh spans ten days, while in Kerala it spans 6-14 days (Arun et al., 2018; Kulkarni et al., 2013; Rahman et al., 2010). The clinical manifestations of Nv infection encompass a wide spectrum, covering asymptomatic cases to those presenting with severe symptoms. Significant clinical features related to Nv infection include breathing difficulties, nausea, vomiting, fever, headache, and acute encephalitis.

Additional symptoms, including behavioural exaggeration, disorientation, pneumonia, and decreased level of consciousness, have been documented in certain patients (Guh et al., 2000; Chua et al., 1999; Wong et al., 2001). During the Kerala outbreak, individuals who were infected exhibited various symptoms, including muscle pain, cough, nervous system disruptions, epilepsy, and encephalitis, in addition to other overall symptoms (Uwishema et al., 2022a; Uwishema et al., 2022b; Uwishema et al., 2022c; Uwishema et al., 2022d; Pradhan et al., 2022). The outbreaks in Bangladesh and India were especially noteworthy for the higher incidence of cases presenting with respiratory discomfort (Yadav et al., 2019).

6. Diagnosis

The timely identification of cases is a crucial factor in effectively controlling the transmission of the virus and reducing its mortality rate. Diagnosis can be conducted in both living patients and deceased individuals. In clinical settings, various samples obtained from live patients, such as swab, cerebrospinal fluid, nasal, blood, throat swab, and urine, can be utilised for the purpose of diagnosing Nv infection. Biopsy samples, such as those obtained from the spleen, kidney, and lung, can be utilised for diagnostic purposes in deceased individuals. Isolating and culturing patients infected with Nv requires the use of upgraded biosafety level 3 and 4 facilities.Numerous diagnostic methods are accessible for identifying Nv, such as virus isolation and neutralization, immunohistochemistry, molecular and serological assays, enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR) (Mazzola et al., 2019). Nv can be cultivated using Vero cells, and within a span of three days, noticeable cytopathic effects become evident (Daniels et al., 2001). Polymerase Chain Reaction (PCR) is considered to be the most sensitive and extensively employed technique for the diagnosis of Nv. Multiple types of polymerase chain reaction (PCR) tests have been created for the detection of Nv. These include traditional reverse transcriptase (RT)-PCR, nested RT-PCR, and real-time RT-PCR. Among these, real-time RT-PCR is the most commonly utilised test and has demonstrated a sensitivity that is 1000 times higher than conventional PCR (Wang et al., 2012). It is important to consider the potential compromise of these techniques in the event of viral genome mutation (Mazzola et al., 2019; Wang et al., 2012). PCR is commonly regarded as the favoured diagnostic method. Nevertheless, when PCR is not accessible, the Nv-specific immunoglobulin M ELISA can serve as a practical alternative (WHO, 2018). Immuno histochemical assays offer post-mortem validation for diagnosing Nv in fatal cases. The confirmation of Nv presence is frequently achieved through viral isolation and neutralization assays, which are exclusively carried out in BSL-4 facilities with rigorous safety protocols (Mazzola et al., 2019).

7. Treatment

The current treatment options for individuals infected with Nv are limited to assistance since there are no authorized therapies available for this infection. Ribavirin and acyclovir have been utilised in previous instances to manage Nv infection. The administration of ribavirin, either intravenously or orally, was observed to result in a substantial reduction of approximately 36% in death rates among patients presenting with Nv encephalitis in Malaysia (Chong et al., 2001). In the context of Singapore, acyclovir was administered to all patients who presented with Nv encephalitis, resulting in a single reported fatality. While there is corroborating evidence regarding the utilization of these medications in the management of Nv, their exact role in Nv treatment remains uncertain (Chong et al., 2001; Broder, 2012). In recent times, there have been continuous investigations conducted to assess the effectiveness of vaccine administration and antiviral therapies in treating Nv infection. This suggests a promising outlook for improved prognosis of Nv in the future (Dawes et al., 2018; Guillaume et al., 2004). Nevertheless, given the elevated mortality rate associated with Nv infection and its significant implications for public health, it is imperative to prioritise the development of targeted antiviral agents to promptly address the needs of those affected (Pradhan et al., 2022).

8. Prevention and Patient Awareness

The significance of patient awareness cannot be overstated when it comes to disease prevention, particularly in light of the absence of a reliable treatment. The primary objective of patient education should centre on promoting strategies to mitigate the risk of contamination or ingestion of date palm sap. The World Health Organisation also advises individuals to refrain from coming into contact with bats and pigs, as well as to avoid consuming fruits that have been bitten by bats or consuming raw date palm sap. It is advisable for individuals engaged in animal slaughter to utilise protective clothing. During an outbreak, it is possible to contain human-to-human transmission by implementing measures that restrict exposure and promote the use of personal protective equipment. The process of contact tracing and implementing quarantines for potential contacts is a significant component of an outbreak response (Shariff, 2019; Wilson et al., 2020; Khan et al., 2012).

9. Conclusion

In the last 20 years, Nv outbreaks have occurred in Malaysia, Singapore, Bangladesh, and, India. Outbreaks of Nv infection pose a substantial danger to the economic and population health of affected countries due to high mortality and migration rates. Expert experts believe Nv could become the next pandemic agent after COVID-19. Hence, public readiness and awareness, particularly in impacted regions, are crucial for controlling and containing Nv epidemics. The proposed measures include banning pig transportation in affected regions and improving sanitation at pig operating centres. Additionally, collaborative efforts should expedite the development of specialized treatment protocols to prevent the spread of Nv.

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Conflict Of Interest

The authors disclose that they do not have any conflicts of interest.

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