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Review Article

Microbiology Section

Nipah Virus: A Threatening Outbreak

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ABSTRACT

Nipah Virus (NiV) first identified in Malaysia in 1998, was found to be a highly pathogenic re-emerging paramyxovirus able to produce febrile encephalitis and respiratory sickness for which there are no vaccinations or approved therapies present. *Pteropus* species bats act as the main natural reservoir. NiV comes under level-4 in biosafety and most commonly spreads through *Pteropus* fruit bat saliva or excrement, or through close contact with intermediate hosts such as pigs. This virus is predominantly common in Southeast Asia and is considered one of the deadliest viruses in the world with the highest mortality rates. Different strains of the virus were found to display different epidemiological and clinical features. In order to contain outbreaks, quick diagnosis and infection control measures are needed. For diagnosis and surveillance, varieties of serological and molecular diagnostic approaches have been developed. Here, the authors review the current concepts in NiV genome, structure, replication, epidemiology, different viral strains, pathogenesis, clinical signs and symptoms, diagnosis, treatment, vaccines and prevention in human beings.

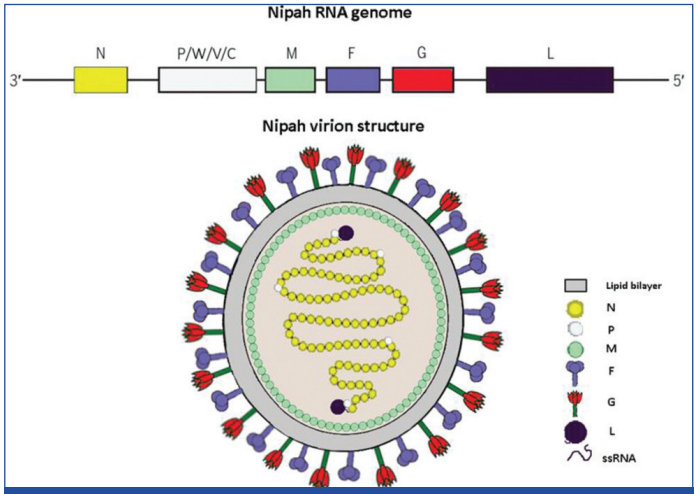
Keywords: Bat saliva, Paramyxovirus, *Pteropus*, Reemerging disease, Zoonotic virus

INTRODUCTION

Emerging infectious diseases pose a huge threat to the wellbeing of both human beings and animals. In the past, viral outbreaks of various kinds have caused all sorts of fear and calamity. Additionally, there has been a global rise in emerging and re-emerging infectious diseases within the last two decades [1]. The detection of the NiV as well as its high case fatality rate (40-70%) highlight the danger of vector-borne diseases in today's globalised society. NiV is classified as a pathogen with a Biosafety Level of 4 (BSL-4) and since it has no available vaccines or therapies, scientists are working hard to ensure it does not cause a pandemic in the near future [2]. The NiV virus, a zoonotic Ribonucleic Acid (RNA) virus belongs to the genus *Henipavirus* from the *Paramyxoviridae* classification [3]. The term "Nipah" originated from a Malaysian village where the virus first appeared in 1998. More than 250 cases of febrile encephalitis involving slaughter house workers were reported during the NiV outbreak in Malaysia. There have been no new outbreaks in Malaysia since then, albeit there have been a few in Bangladesh and India. The latest outbreak was in 2019 to a student from Ernakulam, India [4,5].

The NiV is a pleomorphic enveloped virus (40-1900 nm) that belongs to the *Henipavirus* genus in the *Paramyxoviridae* family. When compared to a typical paramyxovirus, NiV has minor differences in its makeup. Unlike other paramyxoviruses, NiV has reticular cytoplasmic inclusions. Additionally, NiV is larger on average than most paramyxoviruses [6,7]. Many paramyxoviruses have haemagglutinin and neuraminidase characteristics, whereas NiV does not [8]. The [Table/Fig-1] shows the diagrammatic structure of the NiV [9].

The entry of NiV into target cells is achieved through micropinocytosis via the G and F proteins. In addition, it is presumed that the pathway for transcription and replication of the NiV is similar to that of other paramyxoviruses. The arrangement of firmly bound negative sense RNA with N proteins and the RNA polymerase complex is the basic functional component required for replication and transcription. The primary transcription comprises the RNA polymerase complex that is packed inside the virion, which copies the RNA of the virion and afterwards generates, capped, short uncapped RNAs and polyadenylated mRNAs, encoding viral proteins [10-13].



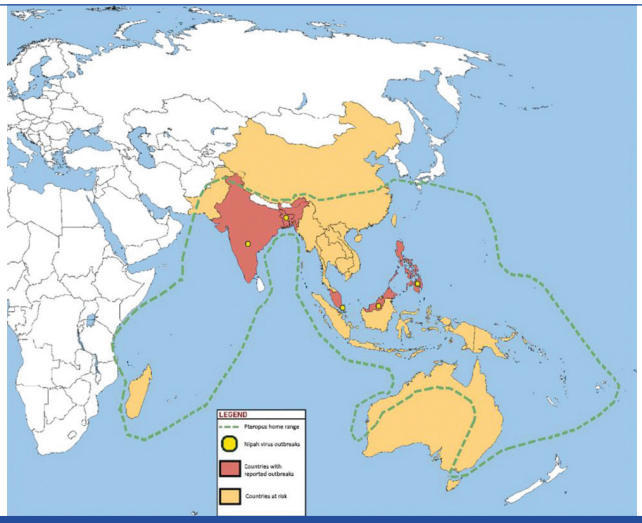
[Table/Fig-1]: Schematic representation of the structure of Nipah Virus (NiV) (lower panel) and the organisation of the genome (upper panel) [9].
Figure was created by the authors using Paint.net

F0 is the precursor that's inactive and produces NiF. This synthesis happens during viral replication, wherein F0 will be broken down by proteolysis into F1 and F2 subunits which is an active form by a host cell protease. F1 and F2 subunits gets transferred to cell surface to get either integrated into budding virions or to enhance the process of fusion between cells that are infected and non infected [14,15]. The fusion process produces syncytia. It facilitates the viral spread in the absence of viral budding [15,16]. The P gene undergoes RNA editing to create two additional non structural proteins, V and W, which are Interferon (IFN) antagonists. In the P gene, the C protein is transcribed from a second open reading frame. NiV was critical to understanding the roles of V,W,P, and proteins in antagonising innate immune responses through a variety of mechanisms [17,18].

EPIDEMIOLOGY AND OUTBREAKS

Epidemiology: *Pteropus* fruit bats also known as flying foxes are thought to be the natural reservoirs for NiV [19]. These bats have been shown to have caused NiV outbreaks in various parts of the world [20,21]. NiV virus is released in the saliva, urine, sperm, excreta of infected bats, but they are symptomless carriers [21,22]. Bats

have been shown to have an adaptive enhanced immune tolerance capable of tolerating disease, hence becoming an asymptomatic viral reservoir [23,24]. *Pteropus* fruit bats from various countries were found to have reactive and antibodies that neutralises NiV during serosurveillance studies [25,26]. In humans and few other animals, NiV had been found to have the tendency to cause deadly infection [Table/Fig-2,3] [27-31].



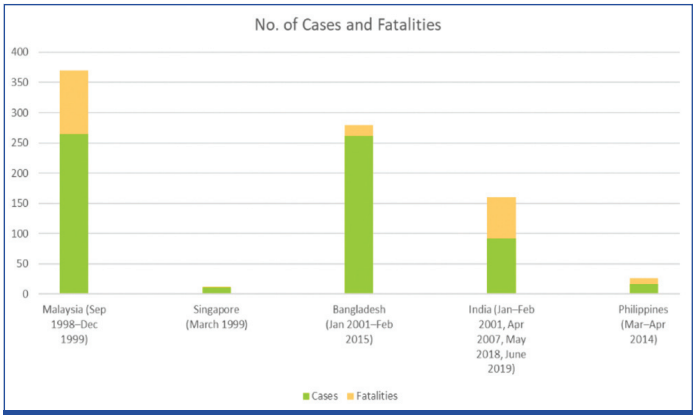
[Table/Fig-2]: Map of Nipah Virus (NiV) outbreaks and *Pteropus* fruit bats distribution [28].
Figure was created by the authors using Paint.net

Region and/or country	Month and year	No. of cases	No. of deaths	Case fatality (%)
1. Malaysia	September 1998-December 1999	265	105	39.6%
2. Singapore	March 1999	11	1	9.1%
3. Siliguri (India)	January-February 2001	66	45	68.2%
4. Meherpur (Bangladesh)	April-May 2001	13	9	69.2%
5. Naogaon (Bangladesh)	January 2003	12	8	66.7%
6. Rajbari, Faridpur (Bangladesh)	January-April 2004	67	50	74.6%
7. Tangail (Bangladesh)	January-March 2005	12	11	91.7%
8. Kushtia, Naogaon, Natore, Pabna, and Thakurgaon (Bangladesh)	January-April 2007	18	9	50%
9. Nadia (India)	April 2007	5	5	100%
10. Manikganj, Rajbari (Bangladesh)	February-April 2008	11	9	81.8%
11. Gaibandha, Rangpur, Nilphamari, and Rajbari (Bangladesh)	January 2009	4	1	25%
12. Faridpur, Rajbari, Gopalganj, and Madaripur (Bangladesh) lalmohirhat, Dinajpur,	February-March 2010	17	15	88.2%
13. Comilla, Nilphamari, and Rangpur (Bangladesh)	January-February 2011	44	40	90.9%
14. Joypurhat (Bangladesh)	January 2012	12	10	83.3%
15. Gaibandha, Manikganj, Naogaon, Natore, and Pabna (Bangladesh)	January-April 2013	24	21	87.5%
16. 13 districts (Bangladesh)	January-February 2014	18	9	50%
17. Philippines	March-May 2014	17	9	52.9%
18. Faridpur, Magura, Natore, Naogaon, Nilphamari, Ponchoghor, and Raibari (Bangladesh)	January-February 2015	9	6	66.7%
19. Kozhikode, Malappuram (India)	May 2018	18	17	94.4%
20. Ernakulam (India)	June 2019	1	0	0
Total		644	380	59%

[Table/Fig-3]: Epidemiological data of Nipah Virus (NiV) [8,29-31].

Malaysia and Singapore: NiV was first identified subsequent to the upsurge of the respiratory system and neurological system involvement in pigs, followed by encephalitis affecting humans [32]. In 1998, various cases with headache, fever and decreased levels of consciousness were observed that was presumed to be caused by Japanese B Encephalitis Virus (JEV) which has a close relation with diseased pigs and also by detecting JEV specific Immunoglobulin M (IgM) in sera of the admitted patients [33]. In response, JEV vaccine and several other protective steps were undertaken, but the disease continued to spread. In addition, the disease affected adult males and have been acquired after close contact with pigs, all of which goes against JEV infection [34]. The fruit bats infecting pigs acted as amplifier hosts, leading to human spread through close contact [35].

Farmers and people handling pig were expelled and slaughtering of pigs in large numbers was performed to reduce the further spread of NiV [36,37]. Dogs were considered to be another risk factor as they were very frequently infected [38,39]. Later in 1999, 11 pig farmers were diagnosed as NiV positive with a single fatality (9.1%) [3,40]. The Government of Singapore has taken immediate and decisive measures against the NiV infection spread, hence the infection rate subsided to a larger extent [Table/Fig-4] [40,41].



[Table/Fig-4]: Total number of cases and fatalities in the different countries affected by NiV outbreaks. Source: Kumar AAK and Kumar AAS, 2018; Sahay RR et al., 2020 [30,31].

Bangladesh: A similar strain of NiV was identified as causing the fatal encephalitis in people in Bangladesh (NiV-B) [42,43]. Since then, seasonal NiV outbreaks exclusively happened in the northwest and central regions.

In the serosurveillance research made, it was noted that the *Pteropus* bats had antibodies to NiV, suggesting that *Pteropus* fruit bats was a natural reservoir for NiV. During the sap-harvesting season, the *Pteropus* bats were licking the sap streams of date palm trees that were being collected. They also get contaminated by urine or faeces of bats, drinking which, caused the transmission of NiV [44-46]. However, NiV transmissions between humans accounted for only 33% and physical contact was identified as the strongest risk factor for causing infection [47,48]. The increased mortality rate and the absence of effective treatments or prevention methods such as vaccines, poses NiV as a significant threat to the health of the people [Table/Fig-4] [49,50].

India: The outbreak in West Bengal failed to detect the aetiology; hence the patient samples retrospectively underwent testing for the presence of NiV virus [51,52]. Majority of the patient's serum samples showed evidence of NiV specific IgM and IgG antibodies. The unidentified index case was hospitalised and further the infection transmitted to 11 hospitalised patients [51]. All these cases were adults who do not have close contact history with pig or other animal but have evidence of nosocomial transmission hence proving the possibility of infection spread from person to person particularly in hospital settings [53].

During the outbreak in Kerala, approximately 300 contact cases were carefully scrutinised for symptoms of NiV. Monoclonal antibodies as a

treatment for NiV arrived from Australia to prevent a sporadic outbreak in addition to rapid diagnosis of the infection, hence controlling and containing the outbreak [Table/Fig-4] [5].

Philippines: In the outbreak that occurred here, the case fatality rate among those who suffered from acute encephalitis syndrome was 82%. Ten patients must have had either close contact with horses or consumed horsemeat. Through, person-to-person transmission, five patients acquired the disease. This outbreak was most likely caused by a strain of NiV-M where there was no previously identified specific person-to-person spread [Table/Fig-4] [34,54].

NiV Strains Associated with Outbreaks

Two NiV strains that are different in their genes have been reported, Bangladesh (NiV-B) with the length of their gene reaching upto 18,256 bp and Malaysia (NiV-M) with a genome length reaching upto 18,246 bp. It was observed that the strains of NiV-M and NiV-B had similarities upto 91.8%, However, their pathogenicity and transmissibility appear to be significantly different [20,42,55,56]. Phylogenetic analysis of the human isolated strain of NiV during a recent outbreak in Kerala (NiV-K) in 2018, showed the length of their gene to be about 18,100 bp, with 96.15% resemblance to NiV-B but still NiV-K has a distinct genetic make-up [57,58]. In contrast, NiV-K gene sequence that encodes NiV G and F had greater similarity with isolates of NiV-B (≥95%) [57].

The NiV-M was seen in *Pteropus hypomelanus*, *Pteropus lylei* and *Pteropus vampyrus*; and NIV-B and NiV-K was found in *Pteropus giganteus*. This must have been possibly due to a coevolution, because the bats which were infected experimentally did not show any symptoms inspite of a high viral load of NiV infection [21]. An infection study made on the African Green Monkey (AGM), NiV-B was observed to have increased pathogenicity in comparison with NiV-M, and the window period for administering passive antibody treatment is narrow for NiV-B [59]. In contrast to NiV-M, NiV-B infection resulted in higher oral shedding during ferret infection studies, as well as increased virus replication in the respiratory tract and rapid onset of productive infection [60,61].

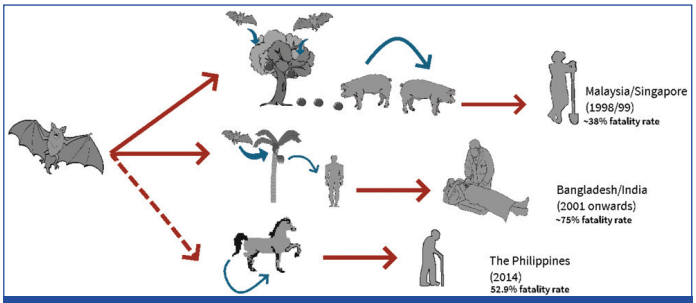
Pigs that have contracted the infection have become the intermediate host for NiV-M, but no intermediate host for NiV-B was found. Unlike NiV-M, NiV-B human infections are spread through consuming viral contaminated raw sap of date palm released by fruit bats infected with NiV. During the NiV-M outbreak, human-to-human transmission was not seen, but it was well recognised in majority of NiV-B outbreaks. Furthermore, NiV-B outbreak case fatality rates were significantly high almost 60-100% than those resulting from NiV-M which is about 39%. This wide difference in mortality rates could be due to the variation in the healthcare aid in various other countries, and also the outbreaks in Bangladesh are commonly detected by retrospective manner [62]. NiV-B has incubation period that is shorter than NiV-M [8]. The majority of patients with NiV-B infection had both respiratory symptoms and fatal encephalitis, while patients with NiV-M mostly only had encephalitis with few signs of respiratory disease [51,63]. Finally, it was seen that NiV-B exhibits increased intra-strain genetic variability [64].

Risk Factors and Mechanism of Transmission of Nipah Virus (NiV)

The NiV, like many other zoonotic infections, has a complex mechanism of transmission varying from region to region. The outbreaks documented in numerous countries around the world have certain similarities and differences in regards to how the virus infects people.

The fruit bat to human and human-to-human routes: When bats belonging to *Pteropus* gene are infected, it results in active infection without clinical disease, making them the natural reservoir of the NiV. Significant factors that facilitate the transmission of NiV are physical proximity with animals that are NiV infected, animals that serve as a reservoir and intake of food that is contaminated [64]. In Bangladesh, the most common route of infection is by the consumption of contaminated fresh sap of date palm which was also supported by an investigation report that indicated several infected patients had a history of consuming raw palm sap prior to the disease onset [65]. More patients were identified during the date palm sap collection period (during December to March) [65]. While there was no experimental proof of outbreaks that are transmitted from person-to-person in Malaysia and Singapore, there was still clear evidence of outbreaks that are transmitted from person-to-person in India and Bangladesh [62,64]. The Bangladesh outbreak was further exacerbated by human-to-human and nosocomial transmission [43,62]. Risk factors include contact with infected secretions, touching, feeding or attending to a person infected with the virus, mainly promoting entry of the virus by respiratory droplets [66]. Physical interaction with a single ill person resulted in transmission through five generations, with a total of 34 individuals [48]. Due to physical human-to-human contact being the highest risk factor for transmission of infection as was shown by the 2004 Faridpur outbreak, extra caution should be demonstrated during the management of these patients.

Route of fruit bats to livestock and then to humans: Environmental changes, sudden change in fruit bat habitat, altered diet, movement and behaviour are all ecological drivers that increase the risk of spread of bat borne viruses such as NiV to domestic animals and humans [67]. A case-control analysis of risk factors of NiV infection in humans at the time of the outbreak in Malaysia found that the primary cause of human NiV infection was close contact with pigs as is the case with pig farmers, where 92% of the patients had direct pig contact. The outbreak was thus halted after pigs from infection zone were killed and appropriate methods of disinfection were implemented [32,39]. Infected pig meat travels through countries that have led to virus transmission to other parts of the world. Various control and experimental studies have strongly proved oral and respiratory routes of NiV transmission [68]. Direct interaction with infected horses, contact with contaminated body fluids and consuming undercooked meat from horses that are infected is proved as the routes of virus transmission to humans in the Philippines. In addition to that, some cases were also believed to be due to human-to-human transmission [54]. The [Table/Fig-5] depicts the diagrammatic representation of NiV transmission.



[Table/Fig-5]: The virus may be transmitted to humans during Nipah outbreaks by an amplifying host {e.g., a horse or pig for Nipah virus (NiV)} or can be transmitted from bats directly to humans via contamination in food, water or the environment [9].
Figure was created by the authors using Paint.net

Pathogenesis

Once the virus reaches the respective host via the oral and nasal pathway, it originally resides in the bronchioles, primarily targeting bronchi epithelium and type II pneumocytes [69,70]. Inflammatory cytokines are produced secondary to infection developing in the respiratory tract epithelium, hence the mobilisation of immune system cells and eventually the initiation of Acute Respiratory Distress Syndrome (ARDS)-like illness [70]. Later, the virus travels from the respiratory epithelium into the endothelial cells present in the lungs. Subsequently, the virus can enter the bloodstream spreading to various organ systems that include central nervous (>90%) and respiratory (62%) systems, while the least involved are the renal, splenic and cardiac systems [70,71]. The NiV G protein

binds to the cellular receptor Ephrin-B2 which are found in high amounts in the brain on endothelium and smooth muscle cells, followed by lungs, prostate and placenta along with blood vessels in various other tissues, this distribution of receptors tells about the characteristics seen in this disease [44].

When the virus enters into the Central Nervous System (CNS), two routes are clearly involved, primarily by hematogenous pathway (through choroid plexus or cerebral blood vessels by inducing vasculitic changes) or by direct invasion of the olfactory nerves, as demonstrated in a porcine model [71]. The Blood-Brain-Barrier (BBB) is compromised and Interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha are more pronounced due to virus invasion of the CNS, that eventually causes neurological signs [70]. NiV's high lethality is due to its avoidance of the innate immune response. Often, the biopsy samples of the brain and other organ obtained from NiV infected patients shows syncytial multinucleated giant endothelial cells which can help distinguish NiV encephalitis from other viral encephalitis [71].

Since, a BSL-4 is needed for research of this virus, studies on pathogenesis are limited [72]. NiV was isolated from Cerebrospinal Fluid (CSF), throat/nasal swabs and urine samples [69,73]. These few researches on NiV showed that the incubation period in most cases was below 15 days, but can be up to four months [60,73].

Clinical Features

NiV infection presents with symptoms from mild to severe. The incubation period typically ranged between 4-14 days after exposure [72]. However, the period varied depending on the country in which the outbreak occurred. During the NiV outbreak in Malaysia, the incubation period was between four days to two months, whereas in Kerala, it was between 6-14 days period of 9.5 days [8,57]. While in Bangladesh, the incubation period was around 10 days. On the other hand, the median incubation period in the Philippines was found to be eight days [54]. Acute encephalitis and respiratory illness are the most common symptoms of the virus, causing it to be a serious threat. Only a small proportion of infected people were found to be asymptomatic [39].

Fever, headache, dyspnoea, myalgia and other prodromal signs and symptoms occur after a brief incubation period [26]. As the disease is progressing, within a week the features of encephalitis would start to emerge, with altered sensorium, hypotonia, segmental myoclonus, areflexia, gaze palsy, limb weakness being the most common [26]. Evidence of necrotising vasculitis was found in the brain of Nipah encephalitis cases which was responsible for the extensive CNS involvement. Many neurons adjacent to vasculitic vessels had eosinophilic cytoplasmic and nuclear viral inclusions, a finding evident in infections caused by other paramyxoviruses. Although, direct neuronal invasion may have a significant role in the pathogenesis of encephalitis, the primary pathology underlying this is widespread ischemia and infarction secondary to vasculitis-induced thrombosis [3,37].

Whereas, in some patients, NiV infections would manifest as respiratory diseases, such as atypical pneumonia or ARDS. Neurological signs may or may not appear in these patients. Septicaemia, gastrointestinal bleeding, renal impairment and other complications are all possible in critically ill patients [3,37,74]. Patients rapidly deteriorate, with coma and eventually facing death. Residual neurological deficits, which range from fatigue to depression, are seen in 20% of survivors [75]. Old age, thrombocytopenia with increased aminotransferases upon admission, and brain stem leisons are all additional contributing factors to the poor prognosis of the disease [63]. The Malaysian strain caused more neurological symptoms unlike the Bangladesh strain which was responsible for respiratory manifestations [32,64,74].

Diagnosis

The initial presenting symptoms of NiV are non specific, and at the time of presentation, the disease is often not suspected to be Nipah. This can delay precise diagnosis of NiV and can create difficulties in outbreak detection. NiV can be diagnosed by diagnostic tests such as molecular and serological assays, virus isolation, histopathology, and immunohistochemistry. Specimens collected from humans have proven to be helpful especially when assessing the cause of a novel outbreak; some of the specimens include throat swab, nasal swab, urine, blood and CSF. NiV can also be cultured efficiently in Vero cells and yields detectable cytopathic effects in about three days [63]. The main investigation modality done is Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) from body fluids and detection of antibody through Enzyme-Linked Immunosorbent Assay (ELISA). However, the sensitivity and specificity of ELISA is slightly less compared to rRT-PCR. Therefore, rRT-PCR is the most preferred choice to diagnose a NiV infection, since it is more rapid, specific and sensitive [75]. rRT-PCR tests for NiV targets the N,M, or P genome segments. Various different kinds of PCR tests for NiV have been invented, but rRT-PCR has been shown to be the most sensitive out of all. Serological tests detect NiV antigens and also the increased levels of IgM and IgG against NiV antigens. IgM ELISA has shown to be the primary NiV serological diagnostic test, accompanied by rRT-PCR which serves as a confirmatory test [76]. BSL-4 facilities are available for serum neutralisation and regarded as a confirmatory diagnostic test. NiV has been placed into risk category 4 and can mostly be treated within BSL-4 facilities because it spreads through aerosols with a high mortality rate in humans. There are currently no effective and sustainable treatments or vaccines accessible. However, the virus can easily be killed and inactivated with detergent use. After the neutralisation of the virus, it is appropriate enough to be dealt through BSL-2 containment if at all the BSL-4 facility is unavailable. Advanced Diffusion Weighted (DW) Magnetic Resonance Imaging (MRI) of the brain has proven to benefit by radiologically confirming the presence of Nipah encephalitis. It has been observed that MRI pattern such as multifocal discrete lesions that spreads all over the brain especially in the deep white matter and subcortical regions of the cerebral hemisphere can be used for differentiating Nipah from other types of encephalitis [77]. It can diagnose exposed individuals even before serological confirmation is available.

Treatment and antivirals in development: There are no specific antivirals or vaccines available; therefore, the treatment for NiV is supportive. However, drugs like ribavirin and acyclovir have been used in the initial outbreaks of NiV happening in Malaysia and Singapore. Ribavirin, a nucleoside inhibitor has shown to reduce the death toll by 36% when infected with NiV. It also helped reduce viremia in patients infected with the virus, whereas the role of acyclovir has been unclear [78]. Despite the fact that both drugs have independent efficacy in-vitro, ribavirin does not prove to decrease mortality in hamster models when combined with chloroquine [79]. Moreover, passive immunotherapy such as a monoclonal antibody that targets the viral G protein has shown some success in various animal models. A successful outcome of an in-vivo study using a fully humanised monoclonal antibody m102.4 against NiV, in a non human primate model points up to the availability of possible drug therapy for NiV in the near future. All the 12 AGMs that received m102.4 which targets the ephrin-B2 and ephrin-B3 receptor binding domain survived the NiV infection, whereas the control subjects who did not receive treatment deteriorated between days eight and 10 after contracting the infection [63]. The survived AGMs have sparked hope towards successful vaccine development. Comparably, human monoclonal antibody h5B3.1 specific to F protein has proved to be effective against NiV infections in ferrets. Currently, there are preclinical trials in progress for the use of mAb in prophylaxis and postexposure. Several more nucleoside inhibitors have been shown to hinder viral replication such as favipiravir (purine analogue and RNA dependent RNA polymerase inhibitor) has been

approved for use in Japan for the treatment of growing influenza strains. An adenosine nucleoside analog prodrug called remdesivir has also shown activity against coronaviruses, filoviruses and paramyxoviruses. It also reduces mortality in non human primates that are infected with Ebola virus as well as in-vitro activity against both NiV and Hendra virus (HeV) [80]. Similar to NiV, HeV are bat-borne zoonotic paramyxoviruses identified in 1990, causing severe systemic, most commonly severe life threatening neurologic and respiratory disease in people and mammalian species [81]. The final nucleoside analogue studied against NiV is 4'-azidocytidine and its prodrug called balapiravir. Balapiravir acts against both NiV and HeV; however, it has shown poor bioavailability and adverse reactions in clinical trials done involving hepatitis C and dengue virus. An IFN inducer called Poly(I)-poly (C12U), has provided efficacy against NiV in-vitro and in hamster models [79].

Vaccines in development: Several vaccines were developed and used in animal models. Many methods have been established for the development of *Henipavirus* treatments that have primarily concentrated on the surface glycoproteins, G and F. The G protein aids in binding to ephrin-B2/B3 as cellular receptors; consequently, the F protein goes through a configurative change that triggers the merger of the viral membrane and the host membrane [82]. One of the vaccines utilises an adjuvant HeV sG protein-based subunit vaccine that has been proved in the protection against both HeV and NiV in rabbits, ferrets, and AGMs [83]. The Hendra Virus-soluble Glycoprotein (HeV-sG) vaccine is mainly used for HeV in horses in Australia to reduce zoonotic infections to humans. Another vaccine uses human monoclonal antibodies for passive prophylaxis; i.e., m102.4 against HeV G and NiV F, it has shown to provide protection against NiV and HeV when given prophylactically and given immediately after exposure [84]. Both the NiV F and G proteins are seen as suitable antigens for protection and they target on vaccine-elicited neutralising antibodies [84]. The development of vector-based vaccines is ongoing, like the ChAdOx1 NiV-B vaccine. All vaccinated hamsters had remained stable throughout the study with no evidence of viral RNA collection from oropharyngeal swabs. Whereas, the control group of hamsters had suffered neurologic deficits, respiratory symptoms and weight loss. Recombinant Vesicular Stomatitis Virus (rVSV) was useful in deriving a vaccine containing the NiV G protein with F protein that's incompatible, in an experiment done with three AGMs showed the following. They were exposed to NiV-M three weeks after being vaccinated against it, all the three monkeys survived a little while with no evidence of clinical disease. However, later on two among the three monkeys had symptoms consisting of raised breathing, and lethargy; they were later tested positive for NiV RNA; but both the monkeys showed recovery later. The control group suffered tremendously, they were displaying histopathologic changes consistent with NiV infection [85]. Mire CE et al., developed a NiV-B vaccine to address the increase in the pathogenicity of NiV-B over NiV-M. Within three weeks, all vaccinated animals developed NiV-B neutralising antibodies and survived without showing infectious signs [86].

Further, a live-attenuated rabies virus-based vaccine against NiV was explored for wildlife. It included study for the robust humoral immune responses induced by rabies-based NiV-B G protein encoded into the rabies virus vector produced seroconversion in test mice [87]. The researchers propose a live-attenuated rabies-NiV hybrid as a potential vaccine for wildlife with the advantage of vaccination against both rabies and NiV [87]. Virus Like Particles (VLPs) has provided a great amount of immunogenicity with both F and G glycoproteins and it also provided protection and neutralising antibodies titers in Syrian golden hamsters from a vaccine using NiV VLPs [88]. Under development is an mRNA vaccine, which encodes the soluble HeV glycoprotein. It has proven to show partial protection against NiV in Syrian hamsters [89].

Prevention

Since, there are no official vaccines available to treat NiV, the most logical way to tackle the virus is by spreading awareness amongst people and instructs them to follow preventive measures. These interventions include a number of methods to combat various forms of virus transmission, such as food-borne, animal-to-human, and human-to-human routes of transmission. Primarily, food-borne transmission; fruits shall be washed before consumption and fruits with visible bite marks should be thrown away. Moreover, Bangladeshi villagers need to avoid consuming fresh raw date sap due to possible contamination with NiV. Techniques also need to be formulated to avoid bats from accessing date palm trees in regions where sap is consumed raw. Skirts were used to prevent exposure of sap of date palm trees [90]. Animal-to-human transmission includes hindering the movement of animals from contaminated farms to other areas and wearing gloves and other protective equipment during slaughtering and culling of potentially sick animals. Human-to-human transmission includes usage of personal protective equipment among healthcare workers, as well as washing hands frequently to limit NiV infections among healthcare providers. Water shortages may have been the cause of healthcare providers being infected with the virus in Bangladesh, so hand washing is critical to avoid the spread of the virus. A patient suspected of a Nipah case should be isolated immediately to minimise exposure. Precautions need to be taken in handling the patients, the deceased, and the specimens [62,91].

CONCLUSION(S)

Overall, outbreaks of the NiV were reported in different regions of the world, posing a major threat to society. The recent outbreak in Kerala (2019) has drawn attention to the virus again and highlights the pandemic potential of the virus. This situation may worsen by a mutation in the virus. The natural reservoir of the disease is bats. From their extensive distribution throughout the world, it is almost certain that we will see even more disease outbreaks caused by bat viruses. Scientific research shows that bats have a unique immune system that drives a faster spread of viruses, increasing its virulence capacity. The high case fatality and the acute course of the disease posed a major challenge in overcoming the virus. Additionally, there is a scarce amount of medication and no signs of an available vaccine. In order for similar in nature sporadic outbreaks to be controlled, studies and research should be conducted when it comes to preventative and containment measures. Educating society, expectancy, and action from the government sectors are all required to restrain the threat posed by NiV.

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