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Nipah virus
The rising epidemic: a review

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SUMMARY

The Nipah virus was discovered twenty years ago, and there is considerable information available regarding the specificities surrounding this virus such as transmission, pathogenesis and genome. Belonging to the Henipavirus genus, this virus can cause fever, encephalitis and respiratory disorders. The first cases were reported in Malaysia and Singapore in 1998, when affected individuals presented with severe febrile encephalitis. Since then, much has been identified about this virus. These single-stranded RNA viruses gain entry into target cells via a process known as macropinocytosis. The viral genome is released into the cell cytoplasm via a cascade of processes that involves conformational changes in G and F proteins which allow for attachment of the viral membrane to the cell membrane. In addition to this, the natural reservoirs of this virus have been identified to be fruit bats from the genus *Pteropus*. Five of the 14 species of bats in Malaysia have been identified as carriers, and this virus affects horses, cats, dogs, pigs and humans. Various mechanisms of transmission have been proposed such as contamination of date palm saps by bat feces and saliva, nosocomial and human-to-human transmissions. Physical contact was identified as the strongest risk factor for developing an infection in the 2004 Faridpur outbreak. Geographically, the virus seems to favor the Indian sub-continent, Indonesia, Southeast Asia, Pakistan, southern China, northern Australia and the Philippines, as demonstrated by the multiple outbreaks in 2001, 2004, 2007, 2012 in Bangladesh, India and Pakistan as well as the initial outbreaks in Malaysia and Singapore. Multiple routes of the viremic spread in the human body have been identified such as the central nervous system (CNS) and respiratory system, while virus levels in the body remain low, detection in the cerebrospinal fluid is comparatively high. The virus follows an incubation period of 4 days to 2 weeks which is followed by the development of symptoms. The primary clinical signs include fever, headache, vomiting and dizziness, while the characteristic symptoms consist of segmental myoclonus, tachycardia, areflexia, hypotonia, abnormal pupillary reflexes and hypertension. The serum neutralization test (SNT) is the gold standard of diagnosis followed by ELISA if SNT cannot be carried out. On the other hand, treatment is supportive since there a lack of effective pharmacological therapy and only one equine vaccine is currently licensed for use. Prevention of outbreaks seems to be a more viable approach until specific therapeutic strategies are devised.

Keywords: Nipah virus, outbreaks, vaccine.

INTRODUCTION

Discovered two decades ago as aetiologic agent of a zoonotic disease, Nipah virus (NiV), is a member of genus Henipavirus in the Paramyxoviridae family. Unlike the Hendra Virus, which is 18234 nucleotides long, NiV is 18246 nucleotides long, which accounts for them to be 15% longer than others in their family. Moreover, the genetic characteristics found in the genus Henipavirus, include the unique, 3′ leader and 5′ trailer sequences, which promote transcription and replication of genomic RNA, respectively [1]. Categorized as Category C priority pathogen by the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID), its clinical manifestations include fever, encephalitis, and in severe conditions, respiratory and pulmonary disorders

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affecting numerous systems of the body [2]. After its discovery from Sungai Nipah (Nipah River Village), where its name originally came from, the first cases characterized by severe febrile encephalitis in humans were reported in Singapore and Malaysia, between 1998 and 1999 [3].
Transmission of NiV has been reported by various ways which include human-to-human transmission and food-borne transmission [2]. The natural reservoir of the virus are bats of genus Pteropus; therefore, proximity with bats is one of the reasons for the occurrence of NiV and swallowing of raw date palm sap is another [1]. Furthermore, the virus spread in Singapore due to handling and holocaust of pigs [4, 5]. The mortality rate was approximately 40% in Malaysia and Singapore, compared to 70% in India and Bangladesh, where the outbreaks of NiV are frequent. Considering its degree of endemic in South Asia, systemic surveillance is required to overcome its recurrence and rising mortality rates [2, 3].

METHODS

Systematic literature review
For this review, a literature search was conducted using PubMed and Google Scholar from their inception to November 2018. The search string included the following keywords: ("Nipah virus") AND ("outbreak" OR "transmission" OR "clinical manifestation" OR "neurologic manifestation" OR "geographic distribution" OR "global distribution" OR "genomic distribution" OR "etiology" OR "causality" OR "genomic structure" OR "pathogenesis" OR "treatment" OR "prevention" OR "control" OR "biosafety" OR "economic burden"). Articles in other than the English language were excluded.

NiV genome, structure and replication
Like all other paramyxoviruses, NiV and HeV are also single-stranded RNA viruses which replicate in the cytoplasm; however, NiV is 12 nucleotides longer than HeV and therefore have the largest genome in their family. Right after its emergence in 1999, Harcourt et al. described the genomic relationship between other paramyxoviruses and NiV. The authors also studied to identify the various genes involved in the genomic making of the virus, which included the nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), and glycoprotein (G) genes [6].
The virus particles are pleomorphic in shape, altering from spherical to filamentous, and have a diameter of approximately between 40 and 600 nm [6]. NiV is covered with a lipid capsule encompassing a nucleocapsid. A single layer of surface projections surrounds NiV envelope, showing the attachment and fusion proteins. The nucleocapsid core comprises of the genomic RNA, nucleocapsid protein, polymerase, and phosphoprotein, while the envelope comprises of the matrix protein which preserves the virion structure. Although members of the paramyxovirus family typically have a genomic length of 15,500 nt, the HeV has a length of 18,234 nt. [7].
Entry of the NiV in the target cells is typically through a process of macropinocytosis via the glycoprotein and fusion protein. The two cellular receptors bound in the process are ephrin-b2 and ephrin-b3, which leads to a conformational change of the G and F proteins. Following the receptor binding F fusion activity is assisted by the glycoprotein via an unknown mechanism, resulting in a conformational change leading to the entry of fusion peptide into the host cell. Afterwards, the viral membrane attaches to the cellular plasma membrane leading to the delivery of the core and the release of the viral genome to the cytoplasm, but before the entry, the M protein shell and N protein need to be disrupted due to an unknown mechanism. Moreover, the pathway to transcription and replication of the Nipah virus is presumed to be similar to those of other paramyxoviruses. The basic functional component needed for the replication and transcription is the combination of tightly bound negative sense RNA with N proteins and RNA polymerase complex. The primary transcription consists of the RNA polymerase complex to be packaged inside the virion, which copies the virion RNA (vRNA) and then generates, capped, short uncapped RNAs and polyadenylated mRNAs, encoding viral proteins [8, 9].

Vectors, transmission and reservoirs
The first cases of Nipah virus were recognized in pigs showing symptoms of respiratory disease and in a few cases, neurological deficits, in 1998 in Malaysia. Most pigs had asymptomatic infections and a majority of them fully recovered. Exposure to ill pigs resulted in transmission to humans where 276 individuals developed encephalitis. Unlike other Paramyxoviruses, the Nipah virus

demonstrates a wide host range, infecting multiple species of animals such as horses, cats, and dogs, as well as humans. The natural reservoirs for the virus are fruit bats from the genus Pteropus. 5 of 14 bat species in Malaysia have been identified as carriers of the virus with *Pteropus hypomelanus* and *Pteropus vampyrus* having the highest rates of seroprevalence with the infectious virus being identified in their urine and saliva. *Pteropus hypomelanus* and *Pteropus lylei* were isolated as being carriers in South and South East Asia. All four species of this genus located in Austria were also identified as being carriers. When bats from this genus are inoculated with Nipah virus, it results in active infection without clinical disease symptoms solidifying their role as reservoirs. There is some evidence to suggest that female bats, in the states of pregnancy and lactation, are more susceptible to infection.

Transmission of the virus takes place horizontally via urine, feces, and saliva. The highest risk of infection in bats, however, occurs when there is nutritional stress due to climate change and habitat loss which alters food sources. There is no evidence to suggest that direct bat to human transmission takes place; instead, the virus spreads via body fluids [8]. In the Bangladesh outbreaks ranging from 2001 to 2008, the transmission methods were identified as contamination of date palm saps by bat feces and saliva, nosocomial transmission, and human to human transmission. The case for the human to human transmission was made by the 2004 Faridpur outbreak where physical contact was identified as the strongest risk factor for developing an infection. Physical contact with a single ill individual resulted in transmission through 5 generations, 34 individuals in total [10].

Geographic distribution

During an outbreak of encephalitis in September 1998 in pig farms of Ipoh in Peninsular Malaysia, which was initially presumed to be due to Japanese encephalitis, the suspected cases isolated were 265, and the virus occupied the region till April 1999 [5, 8]. It initially afflicted pig handlers, and a team of multidisciplinary investigators employed clinical and autopsied findings from 32 fatal human cases of NiV infection; electron and light microscopy confirmed the viral inclusions of NiV. This first outbreak led to a significant economic loss to Malaysia owing to over a million pigs being euthanized, leading to a steep decline in international trade of the region. However, the infection did not remain cornered in Malaysia, and the diseased transmission accelerated when the virus afflicted pigs moved 160 miles in the state of Negri Sembilan. These pigs from Negri Sembilan were kept and slaughtered in an abattoir in Singapore, and the virus subsequently spread to the abattoir workers. An alarming mortality rate of 40% was noted and the majority of patients presented with a severe acute encephalitis syndrome and a proportion of patients presented with pulmonary findings. However, to one's surprise, no new cases have been reported from either Malaysia or Singapore since 1999 [5, 11].

Nevertheless, from 2001 continuing cases of NiV have been reported from Bangladesh and the virus has regrettably disseminated to affect regions of India. The first outbreak in Bangladesh was reported in 2001, from Meherpur district followed by uninterrupted outbreaks in selected regions every year. Moreover, sporadic cases of NiV encephalitis have been reported, up to March 31, 2012, a total of 209 NiV human cases were reported and constituted a mortality rate of 77%. Additionally, two outbreaks of NiV encephalitis in the eastern state of West Bengal in India, bordering Bangladesh have been reported in 2001 and 2007. The mortality rate observed in India was estimated to be 70%. In 2001, the outbreak was observed in Siliguri, West Bengal and the clinical material obtained confirmed Nipah virus-specific immunoglobulin M (IgM) and IgG antibodies in 9 out of 18 patients. The second outbreak in 2007 was in Nadia district of West Bengal. According to the surveillance and outbreak reports by the World Health Organization (WHO) assessing NiV outbreaks in South-East Asia from 2001-2012, the average case fatality rate is 74.5% [8]. However, in the relation of NiV transmission, contrary to the Malaysia-Singapore 1998 outbreak being consistent by a porcine epidemic transforming over time to a human epidemic, the outbreak in Bangladesh has portrayed an on-going NiV transmission from bats to human [10].

Deka M.A. and Morshed N. have outlined the disease transmission in South and South East Asia and coherently linked it to factors predisposing this region for repeated outbreaks of NiV. The analysis demonstrated a favorable environment in vast areas of the Indian sub-continent, Indo-

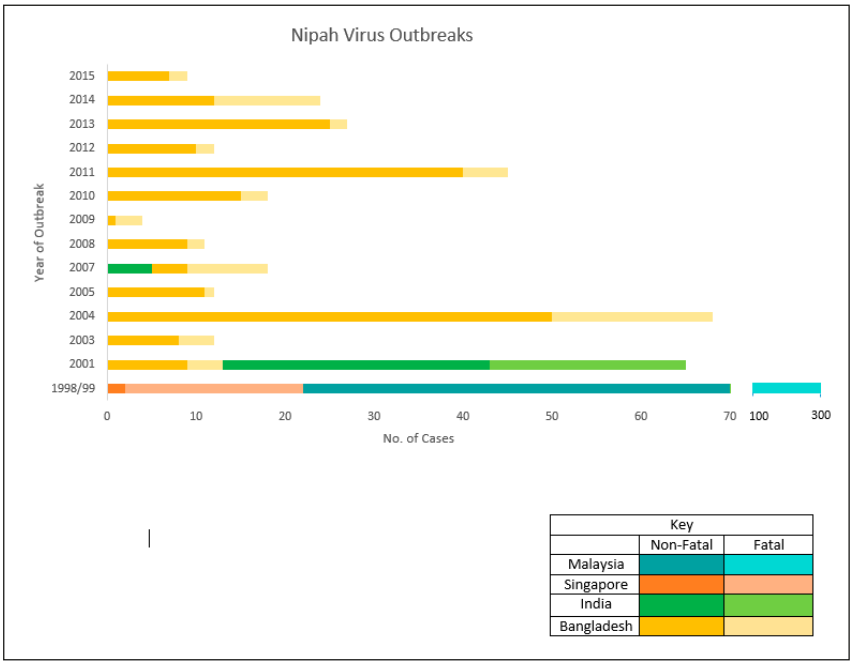

Figure 1 - Number of reported cases and deaths by year due to previous NiV outbreaks.

nesia, Southeast Asia, Pakistan, southern China, northern Australia, and the Philippines. In Bangladesh, NiV causes high mortality rates with the majority of human cases occurring in the central and northwestern districts or the "Nipah Belt", a district in Bangladesh which is significant concerning repeated outbreaks of NiV since 2001 [12]. Until recently, first NiV outbreak cropped up in

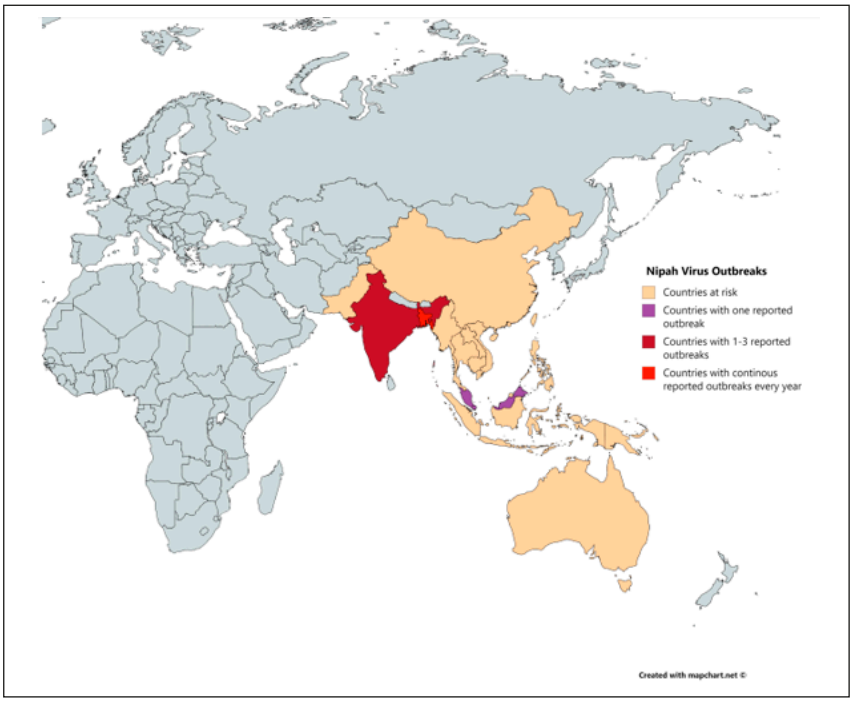

Figure 2 - Global distribution of NiV.

Kerala State of India, and the third outbreak in India after the surge of NiV in 2001 and 2007. Recently in May 2018, Kerala state had a total of 23 NiV cases (18 confirmed and 5 probable), out of which, 16 out of 18 confirmed cases ultimately died. The outbreak was localized to two districts in Kerala State: Kozhikode and Malappuram. However, no new cases or deaths have been reported after this [13]. Finally, sequencing of different NiV isolates revealed that the NiV strains isolated from different hosts in Malaysia were very similar at the genome sequence level, on the contrary, the NiV strains from Bangladesh and India exhibited a greater genetic diversity. The NiV outbreaks and the number of cases in different years have been shown in Figure 1 and Figure 2.

Pathogenesis

NiV upon entering the human body spreads through various routes, which include the central nervous system (CNS) and respiratory system. The viremic spread of the infection involves endothelial cells, epithelial cells, and dendritic cells, while the significant NiV receptors in the human body have been found out to be Ephrin B2 and Ephrin B3 [14].

Despite the low levels of virus detected in humans, the viremic spread is the critical path of diffusion in CNS, and segregation of the virus from the cerebrospinal flood can be achieved. The emblem of Henipavirus infection is damage of the endothelial cells of the small blood vessels, which leads to the advancement of the virus into various organs and through the blood-brain barrier and blood-air barrier, which lead to the spread of the infection in the brain and lungs [15]. As indicated by clinical and autopsy studies, endothelial cell damage is the primary reason of Henipavirus infections which leads to systemic vasculitis of small blood vessels, necrosis and extensive thrombosis [16]. Association with shedding and human-to-human transmission with the Ni-B genotype may be responsible for more critical respiratory forms of the infection. Interestingly, unlike pig monocytes, which were shown to be successfully infected by the virus, human monocytes did bind to the virus but showed no signs of a thriving infection [14, 15].

Two models have been proposed to show the dissemination of the virus within the host. The first model indicates the association between NiV and circulating cells of the body which suggest that the dendritic cells confine the virus, get infected and then pass on the virus to circulating leukocytes. These leukocytes then, without themselves being infected, could trans-infect the virus to endothelial vascular cells. As per the literature, CD169 on human dendritic cells was suggested to execute the trans-infection pathway used by the virus. The second mode of transmission shows the direct entry of the virus into the CNS via olfactory nerves. Even though, this pathway does correlate with a direct entry into the CNS through oropharyngeal innervations, spread within the brain remains questioned [14].

Further possible ways include by the endocytic mechanism of macropinocytosis, but this method needs further investigations. Other than that, low-level replication in human dendritic cells shows that it can spread through adjunct with monocytes and lymphocytes and via cell-free viremia. Epithelial cells can also be a route for the transmission of infection either from the basal membrane or by fusion with neighboring epithelial cells. This route indicates the possible spread of the virus to the lungs other than through the airway route.

In conclusion, no vascular involvement is found in late-onset encephalitis with neuronal cells being the target cells. Neurological relapse can occur in some infected individuals if Henipavirus perseverates in the CNS. The means of spread from the previously infected mucosal tissue to the endothelium of various targeted organs and the CNS remains to be determined. Even though the virus is found in all organs, brain microvascular vessels are the most commonly targeted. Further advancement in the understanding of the virus is needed for the determination of antiviral treatment [14, 15].

Clinical manifestations

Although there is a slight difference in the genomic structure of NiV and HeV, the clinical manifestation of these diseases is very much similar. The clinical symptoms of NiV can lead to grave consequences due to its rapid phase of encephalitis, which leads to a high mortality rate.

Initially, there is an incubation period of 4 days to 2 weeks, after which the symptoms start to develop. The primary clinical signs, characteristic symptoms and severe symptoms are shown in Table 1 [3, 17].

In a randomized controlled trial conducted by Goh et al. among pig farmers in Malaysia showed that almost all patients (n=91/94, 97%) had complaints of fever while 65% experienced headaches. It also showed that more than half of the patients experienced an altered level of consciousness and involvement of the brain system, suggesting that its involvement can lead to death due to post-effects of encephalitis [18]. Patients with a reduced level of consciousness had seizures and visible cerebellar signs along with tachycardia. There was also a dramatic, continuous, segmental myoclonus seen in 56% of the patients with a reduced level of consciousness, which was much higher than the further outbreaks occurring in parts of Bangladesh [19].

Furthermore, due to the involvement of the brainstem, these patients showed essential signs of pinpoint pupils with variable reactivity, abnormal doll's-eye reflex, noticeable vasomotor changes comprising of hypertension and tachycardia suggesting a presence of involvement of the medullary vasomotor part of the brain-stem. Dizziness and vomiting were seen in about one-third of the patients, while a nonproductive cough and myalgia was seen in 14% and 12% patients, respectively. Although, patients who experienced late-onset or relapse encephalitis had a lower mortality (18%) than the ones with acute NiV encephalitis (40%), but the ones with late-onset or relapse experienced higher/worse neurological deficits (61%) than the ones who had acute encephalitis (22%) [18]. Therefore, further investigations and studies need to be conducted to assess the factors related to relapsing of encephalitis to help reduce mortalities due to severe neurological deficits.

Generally, high mortality (40-70%) is seen in patients with NiV. There was a higher number of mortalities (73%) in outbreaks seen in Bangladesh, compared to Malaysia (32%), partly due to better healthcare facilities in Malaysia and partly due to emerging strains of NiV in further outbreaks in Bangladesh, after its original occurrence in Malaysia in 1999.

Diagnosis

The virus was isolated from cultured mammalian tissues after its first outbreak in 1998, which subsequently highlighted the idea of a new infectious etiology. Since then, NiV is internationally recognized as a dangerous zoonotic pathogen for which there is currently no available vaccine or effective treatment. Hence, it imposes the highest level of bio-risk management, which is adequately combatted by using containment approaches commonly designated as bio-security level (BSL) 4 or physical containment (PC) 4 [20].

The laboratory diagnosis of NiV infections includes a wide array of methods. Conventional polymerase chain reaction (PCR) has been widely used in the past for the detection of viral isolates in human and animal reservoirs. However, with advancements in rapid detection methods, tests based on conventional PCR are now considered substandard and no longer in use for diagnostic purposes. In 2004, a specific TaqMan Real-Time PCR (RT-PCR) of the Nipah nucleoprotein was developed to characterize field specimens or laboratory material rapidly. This technique proved to be sensitive and reliable for rapid detection of NiV RNA for diagnosis [21].

Furthermore, Sanger sequencing also played a pivotal role to provide insight into NiV clinical and structural correlates. Sequencing of different NiV isolates revealed NiV strains and, currently, viral isolation is the primary means of virus

Table 1 - Clinical signs and symptoms due to Nipah virus infection.

Primary clinical signs	Fever	Headache	Vomiting	Dizziness
Characteristic symptoms	Segmental myoclonus	Hypertension and tachycardia	Hypotonia and areflexia	Abnormal pupillary reflexes
Severe symptoms	Pulmonary syndrome		Neurological signs	
	Cough		Confusion	
	Diffuse alveolar shadowing and acute respiratory distress syndrome (ARDS)		Motor deficits and reduced level of consciousness	
	Hypoxemia		Seizures	
	Abnormal X-ray chest findings		Abnormal MRI findings	

detection for the confirmation of any new NiV outbreak. Once the virus has been isolated, the subsequent identification of virus isolates can be sought by immunostaining of fixed, infected cells, neutralization with specific antisera, PCR of culture supernatants, and electron microscopy. Nevertheless, it demonstrates limited sensitivity which possibly can be encountered by an adequate quantity of samples. Serological testing has been used in the past by surveillance and control programs after outbreaks for infected animals and premises, particularly for NiV infections in pigs in Malaysia. As a part of serological testing, serum neutralization test (SNT) is still regarded as a gold standard; however, it requires PC4 facilities in the laboratory owing to the BSL4 risk of NiV.

On the contrary, in schematic situations where the PC4 facility is unavailable, ELISA is designated as the most affordable and straightforward method. It is favorable in epidemiological studies and on-going surveillance programs. However, unfortunately, it is reiterated that the ELISA does not have 100 percent specificity. False positives can lead to a potential economic loss for pig farmers while false negatives can aggravate the public health, thus remain as a mainstay of concern [20, 22]. Until recently in 2012, a serum neutralizing test was developed which measured NiV neutralizing antibodies under BSL2 risk management. This method produced higher neutralizing antibody titer in comparison to conventional SNT and required almost 10-fold less serum [23].

Furthermore, since NiV grows in cultured cells to high titers, it is visualized in the medium of infected cells by negative contrast electron microscopy, and it remains as the first method for identification of a new causative agent in disease outbreaks [20, 24].

In 2012, samples were taken in Bangladesh from suspected cases and were confirmed as positive if IgM against NiV was found in samples, if NiV RNA was amplified or if NiV was isolated from samples. Then the genomic sequences from two patients in 2008 and partial genomic sequences from three patients in 2010 were characterized and compared with distinct genomic sequences from patients in Faridpur and Gopalganj district. This led to a standardized genotyping protocol for NiV with an accurate way to classify current and future NiV sequences [25].

During the 2018 outbreak of NiV in Kerala, the first line of testing for the diagnostic purpose was employed as RT-PCR or NiV RNA detection. While the second line testing for research purpose involved detection of anti-NiV IgG and IgM and was carried out by the CDC. Later in the year, the University of Manipal in India along with a company Molbio introduced Truenat Test Chips by Point of Care Real-Time micro-PCR for NiV diagnosis [26]. According to the (CDC) guidelines, a patient with a clinical history of NiV can be diagnosed during the acute phase by virus isolation techniques and real-time polymerase chain reaction (RT-PCR) from the throat and nasal swabs, cerebrospinal fluid, urine, and blood while antibody detection by ELISA (IgG and IgM) can be used later on [27].

Treatment and prevention

Treatment of individuals infected with the NiV is currently limited to supportive care. Due to physical human to human contact being the highest risk factor for transmission of infection, extra caution is demonstrated during the management of these patients. There are no licensed therapeutic interventions for treating the NiV. While antiviral treatment seems to be the obvious choice, current intervention strategies are remarkably few.

Two drugs have been identified, namely: ribavirin and chloroquine however, any therapeutic effect they have has not been definitively established. However, in the case of ribavirin, *in vitro* studies have demonstrated it to be effective against NiV replication. The use of ribavirin was also seen in a male survivor, from the latest Kerala Nipah outbreak, with the absence of any respiratory disorder. Eventually, on day 16 and 26 post onset of illness, the presence of NiV RNA was seen to be in the male survivor's semen, however, the conclusion whether the virus was viable in semen or it can be transmitted through sexual routes could not be drawn [12, 28]. Multiple trials employing Ribavirin have been carried out, but their results have been contradictory. While it reduced mortality by 36% in an older study, recent animal studies suggest that it does not have any clinical benefit [29]. Conversely, the anti-malarial drug chloroquine, was shown to inhibit NiV in cell cultures; however, it was also shown not to have any clinical benefits in recent animal models.

On the other hand, passive immunotherapy with a monoclonal antibody which is specific for viral envelope glycoproteins (NiV G-protein) has offered some success. The human monoclonal antibody (mAb) called m102.4, isolated from a recombinant nae human phage-displayed Fab library has displayed some promise and might be approved for future use. It has been proven to possess potent neutralization activity against the NiV and has demonstrated effective post-exposure therapy in ferrets and primates (nonhuman). When administered 10, 24 or 72 hours after exposure to the virus; it resulted in protection against a 10-fold lethal virus challenge, intratracheally and oral-nasally [30]. In ten instances, individuals exposed to the virus were given m102.4 and did not develop the virus. Therefore, it is essential to recognize that m102.4 has proven to be useful for pre and post exposure prophylaxis before the development of clinical symptoms in animal models. However, once disease onset takes place, it loses its reliability. Additionally, very recently, the nucleoside analog 4′-azidocytidine (4′N_3-C, R1479) and it 2′-monofluoro (2′F-4′N_3-C), and 2′-difluoro (2′diF-4′N_3-C) analogs have demonstrated enhanced antiviral activity against paramyxoviruses including the NiV. To make sure their action was due to non-cytotoxic effects, they were tested on NCI-H358 cells for three and seven days. Minimal toxicity was observed. The 2′ monofluoro analog proved to be the most potent against the NiV, even in human primary small airway cells [31]. Furthermore, another drug of Japanese origin, favipiravir, another nucleoside analog, has shown great promise. In vitro, it managed to reduce viral loads at 250 μM when administered immediately after infection or even up to 24 hours' post-infection. It also managed to fully prevent infection in the hamster model when administered orally. This was achieved by administering the drug twice daily, immediately after the infection via the oral route. It managed to prevent the development of any clinical signs even after 42 days' post-infection [32].

Since vaccines against NiV are not available yet, the most efficient ways to tackle it include creating awareness amongst individuals and following strict preventive measures. These measures include various ways to combat different means of virus transmission which include: food-borne, animal-to-human and human-to-human routes of transmission.

The first area for targeted intervention is food-borne transmission; preventive measures against this include washing and peeling of fruits before consumption and discarding ones with visible signs of bites or tampering [33]. Furthermore, Bangladeshi villagers need to be discouraged from consuming fresh raw date palm sap due to probable contamination with NiV. The general population should be encouraged to cook fluids at temperatures above optimum levels to ensure virus destruction. Methods also need to be devised to prevent bats from accessing date palm trees in regions where sap is consumed raw. Even though these methods are still being assessed for potency and reliability, they may help to prevent the spread of NiV in Bangladesh [10].

Finally, the most widely used preventative measures to reduce the spread of the virus via animal-to-human transmission include restraining the movement of animals from infected farms to other areas and covering hands with gloves during the process of annihilation. Proper cleaning of infected farms with correct detergents is also necessary to prevent the infection from spreading [33]. In low socioeconomic countries like Bangladesh, where the total amount spent on health services per person per year is as low as $ 12, family members provide the most direct health care, even in hospital settings. In such conditions, it should be the responsibility of healthcare staff to ensure that family members of infected individuals realize the importance of handling infected saliva to prevent human-to-human transmission of the infection. Moreover, caregivers and healthcare workers are advised to wash their hands frequently and thoroughly which might be hindered by several reasons, such as scarcity of running water has occurred in one of the hospitals in Bangladesh, which led to the spread of the infection, by the healthcare workers themselves [34]. Therefore, healthcare professionals are advised to treat any Nipah like symptoms as an absolute emergency to prevent the spread of the virus [11, 35].

Vaccines

Initially, recombinant vaccines were used which provided evidence that vaccination could offer complete protection from the virus as NiV envelope glycoproteins elicited an immune response. Since then, multiple vaccination strategies have been proposed. Some of these strategies include

vaccination of swine herds and horses to prevent spread to human populations; however, these would prove ineffective in countries like Bangladesh where fruit bats contaminate food sources too, and hence human vaccines need to be developed. Nonetheless, ALVAC vectored recombinant canarypox vaccine has shown the potential to protect pigs and prevent viral shedding. They also resulted in the induction of high antibody levels [36]. Another strategy would follow the current Ebola vaccination approach where stockpiled vaccines are deployed for ring vaccination around a settlement.

As of 2018, no large-scale NiV clinical trials have been conducted due to the sporadic nature of outbreaks of the virus which prevents the conductance of any such trials. Furthermore, the Food and Drug Administration could allow vaccines that predict efficacy on animal models to translate to human infections, but no vaccine has been approved for use as of yet. All candidate NiV vaccines being developed right now are in the pre-clinical stage as their effectiveness is still being tested on animal models. Several different vaccines which utilize sG protein and differing adjuvants like oligodeoxynucleotide have demonstrated a protective effect in animal models. The most effective vaccine in this group is the Equivac HeV developed with an immune-stimulatory adjuvant. Other vaccines using the outer-membrane G/F proteins have also shown complete protection in hamsters, ferrets, and African Green Monkeys after single injections [37]. Furthermore, vectored VSV vaccines are also being developed, and one has shown cross-protection against NiVb and NiVm [38]. The first and only licensed prophylactic treatment for the NiV which is available is the previously mentioned Equivac HeV. It was released in Australia in 2012 and is an equine vaccine [5].

It should also be noted that the Coalition for Epidemic Preparedness Innovations (CEPI) has awarded twenty-five million US dollars in funding to Profectus BioSciences and Emergent BioSolutions on May 24th, 2018, to collaborate and develop a vaccine for the NiV. This historic action has been taken to combat this lethal disease which currently has a mortality rate of 75% [39].

Economic burden

In the first outbreak of 1999 in Malaysia, NiV had a substantial economic impact on hog raising and the consumption of livestock products. A decade earlier, the consumption of livestock products had a continuous increase, but after the outbreak, this trend declined quickly additionally, since pig export was a significant industry in Malaysia, with a total number of 235 million pigs spread around the country. However, due to the epidemic, the number of pigs and farms rapidly decreased, bringing the ex-farm price from RM4.29/kg (US$1.03/kg) in September 1998, to RM1.29/kg (US$0.31/kg) in the following April, therefore majorly affecting the earnings of farmers. Additionally, in order to prevent the virus from affecting the mass, 1.1 million pigs were culled costing about a total of RM280 million (US$66.8 million)

Moreover, multiple other industries were affected by the outbreak; one sector which suffered the most was the feed industry, which provides the hog raising sector with feeds. The feed industry had a stagnant decline in its production of about RM67 million (US$16 million) [40].

Due to the increasing burden of Nipah around the globe, several countries have developed interventions from any future outbreaks happening in the future, which is an additional economic burden over the countries prevalent to such epidemics. In Bangladesh, many activities such as the cost of creating campaigns, staff cost, materials pre-testing, field visits, and transportation have caused a total damage of 21 million BDT (US$255,000) [41].

Therefore, considering the statistics and the notable economic burden NiV has imposed, if the outbreaks are not controlled, more farms and industries will be affected, creating many future troubles.

CONCLUSION

Despite the several warnings in the past two decades, regular outbreaks of NiV have led to numerous mortalities and morbidities in both humans and animals. Additionally, due to its pandemic potential, the prevention of this disease is of critical importance due to its capability of causing significant physical and economic burden. Therefore, this calls for an urgent need for the health authorities to conduct clinical trials in order to establish possible treatment regimens to prevent any further outbreaks.

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None

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