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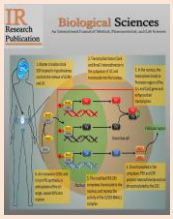

Nipah Virus: Understanding the new emerging global threat

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ABSTRACT

Nipah virus, a newly emerged zoonosis, is caused by flying foxes. It has reported occasional outbreaks of encephalitis and respiratory syndrome and a significant mortality rate. Since 1998, when it was first identified in the Malaysia outbreak, this rare brain-damaging virus infection continues to emerge in different parts of the world. Although the risk of infection is imposed on almost a quarter of the world, due to widely distributed natural hosts, no approved specific treatment and vaccine is available till now, but research continues. Therefore, a detailed discussion of this forthcoming infection needs to be done. This review article focuses on the current scenario of the infection caused by the Nipah virus as well as emphasizes the potential for Nipah virus infection to become a global threat in the future. Further, this article provides a comprehensive review of the infection transmission, its signs and symptoms, diagnosis, and treatment methods with emphasis on prevention and control measures.

Introduction

Factors like modern medical practices, globalisation, accelerating urbanization and environmental factors have led to the emergence of various new infectious diseases including zoonotic diseases—those that pass from animals to humans. Expansion of these newly emerged infectious diseases having high mortality rate, is the current threat faced by the global community. There is an urgent need for a safe and effective vaccine for these diseases to minimize the loss that can be caused in the near future. In the absence of the vaccine, controlling zoonosis particularly in developing countries, which lack the inadequate sanitation and has high animal-human interactions is very important. Nipah virus is one of the best examples of the newly emerging zoonosis that has causes severe disease in both animals and humans. It is a highly pathogenic, biosafety level 4 (BSL4) virus of family Paramyxoviridae, genus Henipavirus (1). This RNA virus is closely related to Hendra virus and Cedar virus, the other two recognized member of the genus Henipavirus. Flying foxes, also known as fruit bats of the genus Pteropus, are the natural reservoir for Nipah virus (1). Nipah virus infection first appeared in domestic pigs in Malaysia in 1998, which infected the pig farmer and people with close contact with the pigs. It was from the village Kampung Sungai Nipah, the first viral isolate was found, and thereafter called as Nipah virus (2). Since the initial outbreak, it has affected humans in different parts of the world. The most recent outbreaks have been reported in India and Bangladesh. With only a few known outbreaks in

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List of abbreviation: *BSL4: Biosafety level 4; CEPI: Coalition for Epidemic Preparedness Innovations; RNA: Ribonucleic acid; OIE: Office International des Epizooties; RT-PCR: Reverse transcription polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay; IgG: Immunoglobulin G; IgM: Immunoglobulin M; WHO: World Health Organization.*

Asia has shown a devastating effect and death on people, making it a serious public health concern. People infected with Nipah virus have shown acute respiratory distress syndrome and lethal illness including coma and fatal encephalitis (1). With a mortality rate between 40% to 100% in both humans and animals, the Nipah virus has emerged as one of the most deadly viruses known to infect humans. It has been listed in the Diseases 2020-(OIE) Terrestrial Animal Health Code, a World Organisation for Animal Health (3). This review article focuses on the current scenario of the infection and the global threat imposed by the Nipah virus in the future.

Transmission

Fruit bats (genus Pteropus, family Pteropodidae) are the natural host for the Nipah virus whereas livestock (pig, horse) is the intermediate host. Both hosts have contributed to the transmission of the Nipah virus to humans. The human infection can be transmitted through bat-to-human, animal-to-human, and human-to-human transmission. Transmission of Nipah virus infection to human beings is represented through Fig. 1 (4). The infected animal can also infect another animal leading to animal-to-animal transmission. In India and Bangladesh outbreaks in 2001, the most likely source of infection in humans was the consumption of fruit or fruit products (fresh date palm sap) which had possibly been contaminated with urine and saliva of infected fruit bats (P.giganteus) (4). The infected fruit bats feed on fruits or fresh date palm sap on pig farms where they leave traces of their urine and saliva. The contaminated fruits and fruit products were exposed to the pigs on the farm infecting the farm pigs. Further, the people coming in close contact with these infected farm pigs get infected (4).

Ninety percent of infected persons in the 1999 Malaysian outbreak had direct contact with the infected pigs, which were infected after consumption of partially eaten fruits by flying foxes (5). Whereas, in 2014, an outbreak characterized by horse-to-human transmission was reported in the Philippines (4). Human-to-human transmission occurs due to the exposure of visitors and healthcare workers to the respiratory secretions, excretions, blood, and tissue of an infected patient, suggesting nosocomial infection. Transmission can also occur due to physical contact with the infected patient who later died. The transmission of infection from a small number of patients to multiple contacts has proposed the concept of "super-spreaders" (4).

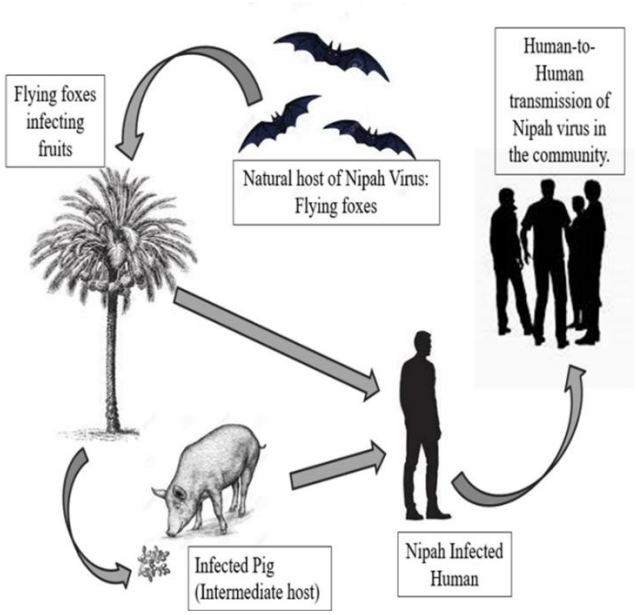

Figure 1. Transmission of Nipah Virus infection in humans.

National and International borders

Nipah virus was first recognized in 1998-1999 during an outbreak of disease recorded simultaneously in humans and pigs in Malaysia (6). From Malaysia, the infection spread to Indonesia and Singapore. Two Indonesian farm workers got infected when visiting a Malaysian pig farm (7) while a subsequent outbreak was reported in the neighboring country Singapore in 1999 while handling the pigs brought from Malaysia (8). That was the beginning of the expansion of the Nipah virus horizon. Since then there have been various outbreaks, all in South Asia, but no new outbreak was reported in Malaysia.

Studies have shown a widespread distribution of both the virus and its vector. There have been 23 species of bats from 10 genera which were found as the carriers of the virus (9). Since bats are gregarious and long-distance flyers, there could be an exchange of viruses with non-migratory ones (10), spreading the virus beyond the physical boundaries of the countries. Scarcity of resource supply could have compelled fruit bats to approach agricultural areas, preceding to transmission of the virus from bat to human. The range of Pteropus giganteus, one of the fruit bats is found in South Asia (11). The

geographical region that comes under the home range of the natural reservoir of the Nipah virus may be at risk for infection and outbreaks. The evidence of the Nipah virus has been found positive in bat samples collected from countries such as Malaysia, Thailand (12), Madagascar (13), India (14), Bangladesh (15), Ghana (16) and Cambodia (17). Evidence of the Nipah-like virus in China (18) and Henipah virus in Australia (19), Papua New Guinea (20), and Indonesia (21) have also been found. This showed the wide distribution of Henipah virus from the east and South East Asia to West Africa covering roughly a quarter of the world population.

During the 1998 to 1999 outbreaks, More than 275 people were affected by the Nipah virus in Malaysia and Singapore. Out of which 40% of the patients suffered from rigorous nervous infirmity and died. A total of 105 deaths were reported in Malaysia whereas in Singapore, out of 11 cases, one fatal case was seen. In the Malaysia outbreak, infection was transferred from the intermediate host- pigs, which were infected due to the virus spill-over by Malaysian flying fox (8). In 2001, outbreaks were recognized in Bangladesh and India, and for the first time, Nipah virus encephalitis was identified in the Meherpur district of Bangladesh. Since then Nipah virus encephalitis has been reported almost every year in the different districts of Bangladesh, mostly in the west and north-western region with high mortality. Till Feb 2015, a total of 261 human cases were reported in Bangladesh, out of which 198 died with a mortality of 76%. Outbreaks reported in a total of 13 districts of Bangladesh in the year 2014, clearly indicate that the Nipah virus has started to extend its boundaries (22).

India has reported 6 outbreaks of Nipah virus encephalitis. The first two outbreaks were in Siliguri (2001) and Nadia (2007), the eastern state of West Bengal bordering Bangladesh. A total of 66 human cases were reported with 45 deaths during the Siliguri outbreak whereas 100% mortality was observed during the Nadia outbreak (5/5) (22). The third outbreak in India was reported in the Kozhikode district of Kerala in May 2018. As of 1 June 2018, 19 human cases were confirmed including 17 deaths in the Kerala outbreak including a nurse who got infected while treating the Nipah infected patient (23). This was the first time an outbreak was reported in Kerala. The fourth outbreak was reported in the Kochi district of Kerala in June 2019 with zero percent mortality. Further fourth and fifth outbreaks were recorded in the Kozhikode district of Kerala with 100% mortality in the September 2021 outbreak and 33% mortality in the September 2023 outbreak. This counted a total of three out of six outbreaks in Kozhikode district and four out of six outbreaks in Kerala state only, which is another indication of the urgency of the development of the Nipah virus vaccine. All the outbreaks in Bangladesh and India were either due to direct contact with fruit bats or indirect contact with the material contaminated by fruit bats.

Outbreaks of Nipah virus in South Asia have a limited geographical range and strong seasonal pattern since all the cases were reported during winter and spring (December-May) (24). All the past reports have shown an occasional increase in the infection zone of the Nipah virus and evidenced the potential of the emergence of disease in the future. The high mortality rate and absence of any effective treatment have made it a significant emerging threat to human health in the WHO South East Asian region. World Health Organisation for Animal Health (Office International des Epizooties: OIE) has included Nipah virus infection in the list of diseases relevant to International Trade (3).

Signs and Symptom

The signs and symptoms of Nipah virus infection have been reported in many mammalian species including swine, dogs, cats, and horses (1). In humans, the infection can be an asymptomatic infection, acute respiratory infection (mild, severe), and even fatal encephalitis. After exposure and incubation of 4 to 14 days, the symptoms start to appear, however, the incubation period may extend up to 45-60 days (29). The influenza-like symptoms of weakness, myalgia, fever, sore throat, and headache are initial symptoms, which can be followed by altered consciousness, feeling abnormally sleepy, and neurological signs that indicate acute encephalitis (Table 2). In acute cases, respiratory syndromes including necrotizing alveolitis with hemorrhage, pulmonary edema, and aspiration pneumonia are seen that may or may not be accompanied by encephalitis and neurological disease (1).

In addition to the lungs, other infected organs are the brain, spleen, and kidney. Septicemia, gastrointestinal bleeding, and renal impairment develop in severe cases (1). Infection of the central nervous system is associated with acute, febrile encephalitis and relapsing encephalitis which may progress into coma in a day or two (30). Residual neurological consequences (persistent convulsion and personality changes) have been noted in approximately 20% of recovered patients. Relapse of

infections may occur even years later (1). In the current outbreak, reported in India (2018), acute respiratory distress syndrome and encephalitis have been observed (24).

Diagnosis

Based on the symptoms various assays for the diagnosis have been developed, the most preferred methods are ELISA and RT-PCR. Early-stage diagnosis involves real-time polymerase chain reaction (RT-PCR) from the throat and nasal swabs, cerebrospinal fluid, urine, and blood. Nipah virus is a single-stranded RNA virus, containing six genes arranged consecutively. The six genes are phosphoprotein, nucleocapsid, attachment glycoprotein, matrix, fusion glycoprotein, and long polymerase. Attachment and fusion glycoprotein are responsible for virion attachment and entry to the host cell (31). Viruses after penetration into the host cell undergo uncoating to release the viral genome into the host cell (32). To neutralize the Nipah virus infection

antibody for fusion glycoprotein is essential. Detection of antibodies (IgG and IgM) can be applied in the outbreaks of disease. In fatal cases, diagnosis is confirmed by immunochemistry on the tissue. Other tests are immunochemistry on the tissues, isolation of the virus by cell culture, and polymerase chain reaction (33). The saliva of an infected person can be used to isolate viral RNA. The high rate of mortality and risk of human-to-human transmission of Nipah virus demands diagnosis to be accurate with a high level of sensitivity and specificity. Validation of existing assays to ensure the accuracy and the development of highly sensitive and specific assays are the demands of the near future.

Treatment

At present, there is no confirmed effective treatment or particular vaccine available for either people or animals. WHO's advice for the management of infected patients involves intensive supportive care along with the symptomatic treatment of severe respiratory and neurological complications caused by the Nipah virus. Supportive treatment should start immediately to maintain the electrolyte and fluid balance whereas the main strategy for the treatment is symptomatic treatments for the management of respiratory failure, cardiac dysfunction, and convulsion. An antiviral drug, Ribavirin may benefit significantly by reducing the mortality rate among patients with encephalitis caused by Nipah virus disease (34).

All the current vaccine candidates for the Nipah virus are in the pre-clinical stage and have shown the feasibility of stimulating a protective immune response in various preclinical challenge models including hamsters, cats, ferrets, African green monkeys, and pigs. Vaccinated animals had shown little or no clinical signs of disease. Experimental subunit vaccine Alhydrogel® has been found to protect against the Nipah virus in multiple animal models (35). Favipiravir (Ravindran, 2018) and human monoclonal antibodies targeting the viral glycoproteins, the m102.4, have also appeared promising in the animal model (36,37). Recently Favipiravir (T-705) has been found to protect against Nipah infection in hamster models (38). Equivac®HeV had been licensed to vaccinate horses in Australia by Pfizer Animal Health against the Hendra virus, a closely related disease to the Nipah virus (39). Studies are going on to find its efficacy on the Nipah virus. On 24 May 2018, CEPI (Coalition for Epidemic Preparedness Innovations) announced a funding of $25 million to Profectus Biosciences and Emergent BioSolutions to develop a human vaccine for Nipah virus infection (40). In February 2020 phase 1 clinical trial of HeV-sG-V, a potent vaccine candidate of Nipah virus was started (41).

Prevention and Control

Due to the lack of effective treatment and high mortality rate, prevention and control of Nipah virus infection are very important. The infection can be prevented by avoiding direct or indirect exposure to the infection by reducing the risk of bat-to-human, animal-to-human, and human-to-human transmission. Additional efforts focused on surveillance and raising awareness of risk factors and preventive measures to prevent future outbreaks. The access of infected bats to the date palm sap should be decreased. Avoid drinking raw date palm juice and consumption of fruit without thorough washing (8,24).

There should be routine cleaning and disinfection of animal farms and all farm equipment. Masks and gloves should be worn during slaughtering and culling procedures, and handling of sick animals. To prevent human-to-human transmission close physical contact with the infected person should be avoided. Both healthcare workers and visitors should wear a masks, gloves, and protective equipment. Standard precaution guidelines by the WHO should be enforced to prevent nosocomial infections (8,24).

Conclusion

Table 1. Mortality and Morbidity due to Nipah-Like or Nipah Virus Encephalitis in South East Asia Region (2001-2021).

Location	Month /Year	Number Infected	Number deaths	Fatality Rate (%)	Ref.
Country: Malaysia					
Kampung Sungai Nipah	1998-1999	265	105	39.62%	(8)
Country: Singapore					
Abattoir worker	1999	11	1	9.09%	(8)
Country: Bangladesh					
Meherpur	April, May 2001	13	9	69%	(22)
Naogaon	January 2003	12	8	67%	(22)
Rajbari Faridpur	Jan 2004 Apr 2004	31 36	23 27	74% 75%	(22)
Tangail	Jan- Mar 2005	12	11	92%	(22)
Thakurgaon Kustia Pabna, Natore and Naogaon	Jan-Feb 2007 Mar 2007 Apr 2007	7 8 3	3 5 1	43% 63% 33%	(22)
Manikgonj Rajbari	Feb 2008 Apr 2008	4 7	4 5	100% 71%	(22)
Gaibandha, Rangpur and Nilphamari Rajbari	Jan 2009	3 1	0 1	0% 100%	(22)
Faridpur Faridpur, Rajbari, Gopalgonj, Kurigram,	Feb-Mar 2010	8 8 1	7 7 1	87.50% 87.50% 100%	(22)
Lalmohirhat, Dinajpur, Rajbari, Comilla Nilphamari, Faridpur,	Jan-Feb 2011	44	40	91%	(22)
Joypurhat	Jan 2012	12	10	83%	(22)
Pabna, Natore, Naogaon, Gaibandha, Manikganj	Jan- Apr 2013	24	21	88%	(22)
13 districts	Jan-Feb 2014	18	9	50%	(22)
Nilphamari, Ponchoghor, Faridpur, Magura, Naugaon, Rajbari	Jan-Feb 2015	9	6	67%	(22)
Country: India					
Siliguri	Feb 2001	66	45	68%	(22)
Nadia	Apr 2007	5	5	100%	(22)
Kerala (Kozhikode and Malappuram)	May-June 2018	19	17	89.5%	(25)
Kerala (Kochi)	June 2019	1	0	0%	(26)
Kerala (Kozhikode)	Sep 2021	1	1	100%	(27)
Kerala (Kozhikode)	Sep* 2023	6	2	33%	(28)

*As of 30 Sep 2023.

Table 2. Sign and Symptom of Nipah virus Infection in Humans.

Sing and symptom of Nipah virus infection	
Early stages	Fever, Vomiting, Cough, Headache, Stomach Pain
Advanced stages	Myalgia, Sleepiness, Epilepsy, Fatigue, Fainting, Nausea, Convulsions, Lethargy, Choking, Respiratory illness, Encephalitis, Disorientation, Mental confusion, Coma, Potential death

A recent outbreak in South India has renewed the reminder of the silent threat possessed by the deadly Nipah virus. This little-known virus was discovered 20 years ago and could become the next global pandemic. Nipah virus circulates among fruit bats that have a wider home range, and pose the risk of infection to almost a quarter of the world. The capability of Nipah infection to spread easily through human-to-human transmission, especially in developing countries where sanitation and hygiene are a big problem, is a matter of concern.

Although only a few outbreaks have been reported in Malaysia, Singapore, Bangladesh, and India, the fatality rate was high. Depending upon the adequate healthcare facilities and the severity of the clinical manifestation, a mortality rate of range 40% to 70% has been seen. Bangladesh has experienced Nipah virus outbreaks almost every year since 2001. High mortality rate, severe lethal illness, absence of the vaccine, and increasing infection location are alarming situations, hence the urgency of the Nipah virus challenges currently confronting the global community cannot be ignored. World Health Organization has already listed it as a high priority for research. Experimental vaccines for the Nipah virus are in the pre-clinical stage and have been found effective in animal models (35). In addition to developing vaccines and drugs, the improvement of healthcare facilities is also very important for reducing the global risk of Nipah infection. Strong surveillance systems to diagnose new pathogens, safe disposal of infected material, and patient isolation for the early detection and control of Nipah infection are urgent highlights. This review article highlights the silently rising wings of Nipah virus infection which can become a serious global threat in the upcoming year with significant consequences.

Contribution of authors

Not applicable

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Conflict of Interest

None declared

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