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SECOND WAVE OF NIPAH VIRUS IN SOUTH INDIA AND EMPHASIZING "ONE HEALTH" APPROACH TO ENSURE GLOBAL HEALTH SECURITY

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ABSTRACT

Nipah virus (NiV) encephalitis first reported in "Sungai Nipah" in Malaysia in 1999 has emerged as a global public health threat in the Southeast Asia region. From 1998 to 2018, more than 630 cases of NiV human infections were reported. NiV is transmitted by zoonotic (from bats to humans, or from bats to pigs, and then to humans) as well as human-to-human routes. Deforestation and urbanization of some areas have contributed to greater overlap between human and bat habitats resulting in NiV outbreaks. Common symptoms of NiV infection in humans are similar to that of influenza such as fever and muscle pain and in some cases, the inflammation of the brain occurs leading to encephalitis. In May 2018 in Kerala for the first time has killed over 17 people in 7 days with high case fatality and highlighted the importance of One Health approach. Though the first phase of infection is controlled successfully, in the first week of june 2019 again positive Nipah virus is reported in Kochi,Kerala . The diagnosis is often not suspected at the time of presentation and creates challenges in outbreak detection, timely control measures, and outbreak response activities. There are currently no drugs or vaccines specific for Nipah virus infection although WHO has identified Nipah as a priority disease for the WHO Research and Development Blueprint. Antivirals (Ribavirin), biologicals, immunomodulators, and intensive supportive care are the mainstay to treat severe respiratory and neurologic complications. There is a great need for strengthening animal health surveillance system, using a One Health approach, to detect new cases and provide early warning for veterinary and human public health authorities.

INTRODUCTION

Nipah virus (NiV) encephalitis is an emerging infectious disease of public health importance in the World Health Organization (WHO) Southeast Asia region. NiV is an enveloped, negative-sense, single-stranded RNA virus in the family Paramyxoviridae, genus henipavirus. The name of the virus and disease is from the village of "Sungai Nipah" in Malaysia where the virus was recognized in 1999 during an outbreak among pig farmers. Both animal-to-human and human-to-human transmission have been documented.

From 1998 to 2015, more than 600 cases of NiV human infections were reported. Subsequent outbreaks in India and Bangladesh have occurred with high case fatality. A total of 276 cases were reported with 106 fatalities (38%) in Malaysia, but case fatalities in later outbreaks in India and Bangladesh were associated with significantly higher case fatality rates of 43–100%. In May 2018 in Kerala for the first time has killed over 17 people in 7 days with high case fatality including health care professionals. NiV infection in humans has a range of clinical presentations, from asymptomatic infection to acute respiratory syndrome and fatal encephalitis. The natural reservoir of the virus consists of the widely distributed fruit bats from the Pteropodidae family. Virus transmission from bats to humans occurs through inhalation, contact, or consumption of NiV contaminated foods. NiV is transmitted by zoonotic (from bats to humans, or from bats to pigs, and then to humans) as well as human-to-human routes. Human-to-human transmission is particularly notable in the outbreaks in India and Bangladesh, where it has been reported to account for 75 and 51% of cases, respectively. At present no vaccines or antiviral drugs are available for NiV disease and the treatment is just supportive. Current prevention strategies focus on raising disease awareness in affected areas.

Historical Perspective: From 1998 to 2018

NiV was first recognized in 1999 during an outbreak among pig farmers in Kampung Sungai Nipah, Malaysia. Human NiV infection was first recognized in a large outbreak of 276 reported cases in Peninsular Malaysia and Singapore from September 1998 through May 1999. But there are no new outbreaks that have been reported in Malaysia and Singapore since 1999. Three years later, a genetically distinct NiV independently emerged in India as well as in Bangladesh, where human NiV outbreak events have been reported nearly every year since. A putative NiV also caused an outbreak of the disease in horses and people in the Philippines in 2014. NiV was first recognized in Bangladesh in 2001 and nearly annual outbreaks have occurred in that country with periodic disease events in eastern India bordering to Bangladesh. Other regions may be at risk for NiV infection, as serologic evidence for NiV has been found in the known natural reservoir namely Pteropus bats . A second outbreak was reported in 2007 in Nadia district of West Bengal. Thirty cases of fever with acute respiratory distress and/or neurological symptoms were reported and five cases were fatal.

Virology

NiV was first isolated by Chua *et al*. in 1999 after a severe outbreak of viral encephalitis among pig farmers in Malaysia. The virus, cultured from the cerebrospinal fluid of two patients, was causing the syncytial formation of Vero cells after 5 days, and it was found to be a previously undescribed paramyxovirus related to the Hendra virus (HeV). The henipavirus genus in the subfamily Paramyxovirinae (family Paramyxoviridae) was then created for these two pathogenic viruses, HeV and NiV. Subsequently, other viruses were added to this genus. NiV is an enveloped, negative-sense, single-stranded RNA virus. The genome is unusually large, comprising more than 18,000 nucleotides.

Reservoir of virus

Fruit bats of the genus Pteropus have been identified as natural reservoirs of NiV. NiV has been isolated from the brain and spinal fluid of victims in Malaysia. Infective virus has also been isolated from environmental samples of bat urine and partially eaten fruit in Malaysia. Given the distribution of the locally abundant fruit bats in South Asia, NiV outbreaks are likely to continue to occur in affected countries. The bats are migratory. This has generated intensive surveillance for evidence of NiV infection in bats in these countries. NiV has been isolated from Lyle's flying fox (*Pteropus lylei*) in Cambodia. Antibodies to a Nipah-like virus have been found in sera from fruit bats collected in India, Indonesia.

Mode of transmission

Infected bats shed virus in their excretion and secretion such as saliva, urine, semen, and excreta, but they are symptomless carriers. The NiV is highly contagious among pigs, spread by coughing. Direct contact with infected pigs was identified as the predominant mode of transmission in humans when it was

first recognized in a large outbreak in Malaysia in 1999. Ninety percent of the infected people in the 1998–1999 outbreaks were pig farmers or had contact with pigs.

There is strong evidence that emergence of bat-related viral infection communicable to humans and animals has been attributed to the loss of natural habitats of bats. As the flying fox habitat is destroyed by human activity, the bats get stressed and hungry, their immune system gets weaker, their virus load goes up, and a lot of virus spills out in their urine and saliva. Similar fluctuation of virus shedding may be associated with the stressful physiological conditions or seasons.

There were focal outbreaks of NiV in Bangladesh and India in 2001 during winter. Drinking of fresh date palm sap, possibly contaminated by fruit bats (*P. giganteus*) during the winter season, may have been responsible for indirect transmission of NiV to humans. The consumption of date palm sap (which is also known as toddy, kallu, tuak, and tuba in other countries) is popular in a number of Southeast Asian countries, including Bangladesh, India, Indonesia, and Thailand as well as countries such as Malaysia and the Philippines. Fruit bats also consume date palm sap and can contaminate it with saliva, urine, and faeces. This is the means by which NiV is thought to be transmitted from infected fruit bats to humans.

There is circumstantial evidence of human-to-human transmission in India in 2001. During the outbreak in Siliguri, 33 health workers and hospital visitors became ill after exposure to patients hospitalized with NiV illness, suggesting nosocomial infection.

CLINICAL PRESENTATION

Symptoms of NiV infection in humans are similar to that of influenza such as fever and muscle pain. In some cases, inflammation of the brain occurs leading to disorientation or coma. Encephalitis may present as acute or late onset. The latter may be difficult to diagnose because exposure may have taken place several months earlier. Further, those who may have recovered from an acute episode may also have a relapse. Nevertheless, magnetic resonance of the brain is helpful in differentiating Nipah encephalitis from other encephalitis as well as in defining between acute and late onset or a relapsed form of the disease. The brain magnetic resonance imaging in relapsing encephalitis shows more extensive and confluent hyperintense cortical lesions.

In the majority of cases, the incubation period of Nipah has been reported to be 5 days to 2 weeks; however, a maximum delay of 2 months between exposure and the onset of illness has also been observed during the outbreak in Malaysia. There was a high case fatality in the recurrent epidemics in Bangladesh.

DIAGNOSIS

Initial signs and symptoms of NiV infection are nonspecific, and the diagnosis is often not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection and institution of effective and timely infection control measures and outbreak response activities. In addition, clinical sample quality, quantity, type, the timing of collection, and the time necessary to transfer samples from patients to the laboratory can affect the accuracy of laboratory results.

NiV infection can be diagnosed together with clinical history during the acute and convalescent phase of the disease. Main tests including RT-PCR from bodily fluids as well as antibody detection via enzyme-linked immunosorbent assay (ELISA). Different tests include:

- ELISA
- PCR assay
- Virus isolation by cell culture.

NiV is classified internationally as a biosecurity level 4 agent, and the laboratory at National Institute of Virology (ICMR), Pune, India is prepared to diagnose NiV in the country.

Antiviral drugs

Ribavirin

Ribavirin is a broad-spectrum nucleoside antimetabolite antiviral drug that features on the WHO Essential Medicines List. An inhalation solution of ribavirin is also indicated for the treatment, in young children, of severe lower respiratory tract infections due to the respiratory syncytial virus, another paramyxovirus.

Biologicals

Convalescent plasma

The recent pathogen outbreaks, such as Ebola viral disease or Middle East respiratory syndrome coronavirus, have renewed attention to convalescent plasma and immunoglobulins. In case of severe disease, when no treatment with a proven record of safety and efficacy is available, they may appear as the only available therapeutic option.

MONOCLONAL ANTIBODIES

Monoclonal antibodies targeting the surface glycoproteins of HeV have shown efficacy against both HeV and NiV as pre- and postexposure prophylaxis in animal models, but as these antibodies must be administered before the onset of clinical signs, they are unlikely to be useful for treating symptomatic patients, while probably beneficial for postexposure prophylaxis in potentially exposed individuals.

Adjunctive therapies

As for other severe diseases of viral origin, aggressive supportive care may help improve patient survival. NiV infections, especially as seen in Bangladesh, are associated to respiratory disease and respiratory failure. Oxygen supplementation and eventually transfer to ICU are part of the management guidelines of this infection. Ensuring patient access to the best medical practices in this area should remain a priority.

NIV Surveillance and Prevention Strategies

Controlling NiV in domestic animals

Currently, there are no vaccines available against NiV. Routine and thorough cleaning and disinfection of pig farms (with appropriate detergents) may be effective in preventing infection. If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals – with close supervision of burial or incineration of carcasses – may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease. As NiV outbreaks in domestic animals have preceded human cases, establishing an animal health surveillance system, using a One Health approach, to detect new cases is essential in providing early warning for veterinary and human public health authorities.

Reducing the risk of infection in people

In the absence of a licensed vaccine, the only way to reduce infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to and decrease infection from NiV.

Controlling infection in healthcare settings

Healthcare workers caring for patients with suspected or confirmed NiV infection, or handling specimens from them, should implement standard infection control precautions for all patients at all times. As human-to-human transmission in particular nosocomial transmission has been reported, contact and droplet precautions should be used in addition to standard precautions. Samples taken from people and

animals with suspected NiV infection should be handled by trained staff working in suitably equipped laboratories.

"One Health" Approach for NiV Epidemic

The One Health initiative is a growing movement to promote collaboration between the fields of medicine, veterinary medicine, and environmental sciences to improve the interconnected health of people, animals, and ecosyst ems.The importance of such an approach is particularly obvious in the field of infectious disease, as 75% of all emerging infectious diseases are zoonotic. NiV exemplifies the need for a One Health approach. The first known outbreak in Malaysia in 1998, killed 105 people and required the culling of over one million pigs. The virus initially causes fever, headaches, and vomiting in infected people, which can progress to severe encephalitis (inflammation of the brain), respiratory disease, and often death.

Interactions between humans, animals, and the environment are key factors behind NiV outbreaks. Deforestation and urbanization of some areas in Bangladesh have contributed to greater overlap between human and bat habitats. By promoting human–bat interactions, this overlap can increase the risk of "spillover" events, with NiV crossing the species barrier and infecting people.

The current June 2019 and May 2018 outbreak in Kerala, southern India

The outbreak occurred in Kerala state, which has a population of 34 million. The first index case was detected in Perambra (Kozhikode district) in May 2018 where the three members of a family have died in the process of cleaning the old well infected by the bats. Along with infection from bats, there are some nosocomial infections and a total of 11 (8 from Kozhikode District and 3 from Malappuram District) people died out of 13 confirmed cases. A multidisciplinary Central team from National Centre for Disease Control, including Epidemiologist, Pulmonologist, Emergency Medicine specialist, an expert in Zoonosis and Animal Husbandry, was set up for investigation. The field team has advised hospitals to follow intracranial pressure guidelines; use personal protective equipment (PPE) for healthcare workers and sample collection; assist in enhancing active fever surveillance in the community; strengthen contact tracing in close contacts of cases, relatives, healthcare workers; ensure isolation facilities, ventilator support, and hospital infection control practices; and coordinate with animal sector and enhance surveillance for unusual illness and deaths in animals. Appropriate steps to contain this virus have been taken among domestic animals such as pigs. All the contacts are under observation and steps to avoid exposure through animal vectors have been taken and efforts are in place to reduce the panic created by social media by educating people that NiV is not an airborne infection and there is no risk of contracting disease without coming in contact with an infected person. The Kerala government has confirmed one case of Nipah Virus in kochi on 4th June 2019 and 86 people have been kept under observation.

Global Initiatives and Implications for Global Health Security

Deadly epidemics have been threatening humanity since our earliest days. The recent 2013–2016 outbreak of Ebola virus disease in West Africa and the Zika virus in South America in 2016 taught us a lesson: Epidemics can only be prevented when health systems are prepared for them. The Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, with support from the Wellcome Trust and in collaboration with the WHO, has been tasked with facilitating the collaborative development of a draft "Nipah R&D Roadmap" to prioritize the development of diagnostics, therapeutics, and vaccines that are most needed by Nipah-affected countries.

The WHO's International Health Regulations (IHR) aim to provide a legal framework for the prevention, detection, and containment of public health risks at source, before they spread across borders, through the collaborative actions of States Parties and WHO. There is a close link between globalization, urbanization, and the behavior of emerging viruses in the modern era, which can be addressed well through "One Health." Approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multipronged, multilateral collaborative efforts that actively engage local, regional, national, and global levels.

CONCLUSIONS

Currently, NiV is an emerging infectious disease of public health significance for the countries in the Southeast Asia region, which is a natural habitat for the fruit bats. As NiV can be transmitted by various methods, there is a potential public health threat globally. Because NiV is an issue to be addressed by multiple stakeholders to promote health to all citizens, the concept of global health diplomacy holds a great promise to address the needs of global health security through its binding or nonbinding instruments enforced by the global governance institutions. The ministries of health and stakeholders need to work together to develop a vaccine and ensure health security from this bat-borne disease. There is a great need to strengthen intersectoral coordination, review the treatment procedures, infection control practices, and ensure use of PPE and availability of drugs to handle the suspected cases in a better way.

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