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NIPAH VIRUS AN OVERVIEW

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ABSTRACT

Nipah virus, is a paramyxovirus related to the Hendra virus, first emerged in Malaysia in 1998. Clinical presentation ranges from the asymptomatic infection to fatal encephalitis. Malaysia has no more cases since 1999, but outbreaks continue to occur in the Bangladesh and India. In the Malaysia-Singapore outbreak, transmission occurred primarily through contact with pigs, whereas in Bangladesh and India, it is associated with ingestion of contaminated date palm sap and the human-to-human transmission. Bats are a main reservoir for this virus, which can cause of disease in humans and animals. There are currently no effective therapeutics, or supportive care and prevention are the main stays of management.

KEYWORDS: Nipah, outbreaks, encephalitis.

INTRODUCTION

The first cases began in an late September 1998 in the villages near the city of Ipoh in the state of Perak, West Malaysia, where pig farming was a major industry. Cases continued to occur in this region until early for February 1999. The second cluster occurred near Sikamat, a small town in different state, Negri Sembilan, in December 1998 and January 1999. The third or largest cluster began near the city of Bukit Pelandok in the same state in an December 1998.[1] At first, the cases were ascribed to the Japanese B encephalitis [JE], which had previously caused porcine-associated outbreaks in the Malaysia, because of 4 serum

samples the from 28 patients in that outbreak area tested positive for JE-specific IgM, and JE nucleic acids were detected in some of the patients' sera.[2] Thus, the initial measures consisted of fogging to kill mosquitoes and stepping up of JE immunization.[1]

However, features of this outbreak were atypical of JE[3], and most patients were adult males rather than of children. A high proportion of victims had direct physical contact with the pigs, unlike in case of a mosquito-borne disease. Clustering of symptomatic the cases among members of a same household was as high as 33%[1], suggesting an a attack rate higher than that of a JE virus, which are symptomatic in an only 1 of 300 infected individuals.[4] In addition, many patients had previously been immunized against JE, or anti-JE measures failed to stop the increase in the new cases. Furthermore, there were reports of sick animals, with ill pigs developing a severe barking cough and many dying from a disease, which was also not a feature of the JE.[5] A look at the distribution of affected villages was striking, as there were no cases was reported from of Malay villages, despite their close proximity to adjacent the Chinese farms that had encephalitis cases. Malays, is a largest ethnic group in Malaysia, are predominantly Muslims and are forbidden from having any close contact with the pigs or pig products.[6]

In early a March 1999, virologists from a University of the Malaya isolated a virus that, judging by its appearance, belonged to an family Paramyxoviridae, which does not include the JE virus. Further testing showed the virus reacting with antibodies to a Hendra virus, and subsequent sequencing of the viral genome at Centers for Disease Control or Prevention showed the new virus to be about 20% different from a Hendra virus.[7] Once it was established that the cause of a outbreak was a completely new virus, and its association withthe pigs was recognized, completely different measures were that are taken. People working on the pig farms were given a health education or advice via radio or television on the personal protection, including barrier precautions and hand washing after a handling of animals, or disinfection of their environment. Pig-culling operations were conducted in the all infected pig farms in a outbreak areas. In the phase I, which is involved culling in a areas where outbreak cases had be occurred, more than a 1 million pigs were is culled. Phase II involved surveillance in an all pig farms throughout the country. Farms at which ≥3 samples had positive results of testing for Nipah virus [NiV] were considered to be positive farms, or all pigs at the affected farms and at farms within a 500-m radius were culled. This process was carried out for a 3 months.[8] A last human fatality occurred on 27 May 1999. By then,

265 cases of a acute NiV encephalitis with the 105 deaths had been recorded in the Malaysia. In the meantime, a late February, the outbreak had spread to in Singapore, which at that time, imported live pigs from a Malaysia. Four cases of encephalitis admitted within the few days of each other to 3 different hospitals were noted to be a abattoir workers. A Ministry of Health [MOH] was notified. Initially, importation of the pigs from a farms in Negri Sembilan was stopped on 3 March 1999, or/& on 19 March 1999, all pig importation from the Malaysia was suspended and a 2 abattoirs in Singapore were has closed down for the investigation and thorough disinfection. More than the 500 abattoir workers were screened at a Communicable Diseases Centre [Singapore] in the following week, and those with fever or symptoms & signs of the respiratory and neurological disease were admitted to the hospital for investigation and management. An additional 7 identified patients, as well as a 4 index cases, were confirmed to have the acute Nipah virus infection, based on a raised IgM in the serum. Nipah virus [NiV] was also identified by reverse transcriptase PCR in a cerebrospinal fluid [CSF] and tissue of a patient who died.[9] All 11 case patients worked at the 1 of 2 Singaporean abattoirs, or the case-control study showed that significantly more case patients than control subjects had contact with live pigs. Pigs from the Nipah-affected areas of a Malaysia were imported or slaughtered 2 to 3 weeks before the development of a disease in the patients, which would be consistent with the expected incubation period of a paramyxovirus. This of a together with the nucleotide sequences of reverse transcription-PCR [RT-PCR] products the isolated from a Singaporean cases being identical to the Nipah virus sequences from Malaysian cases or pigs[10], established the causal association between human Nipah virus infection in the Singapore or pigs from the Malaysia.

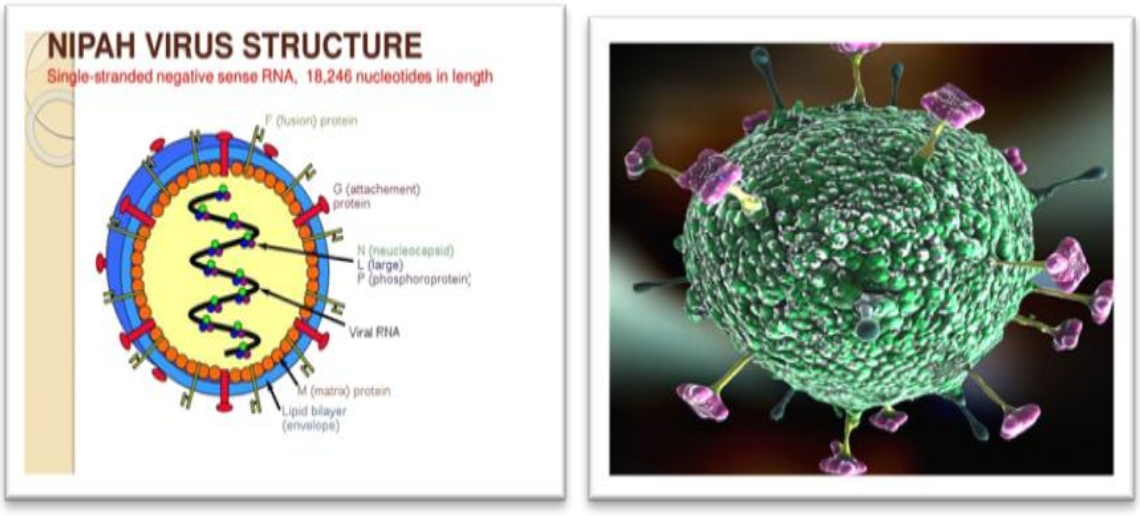


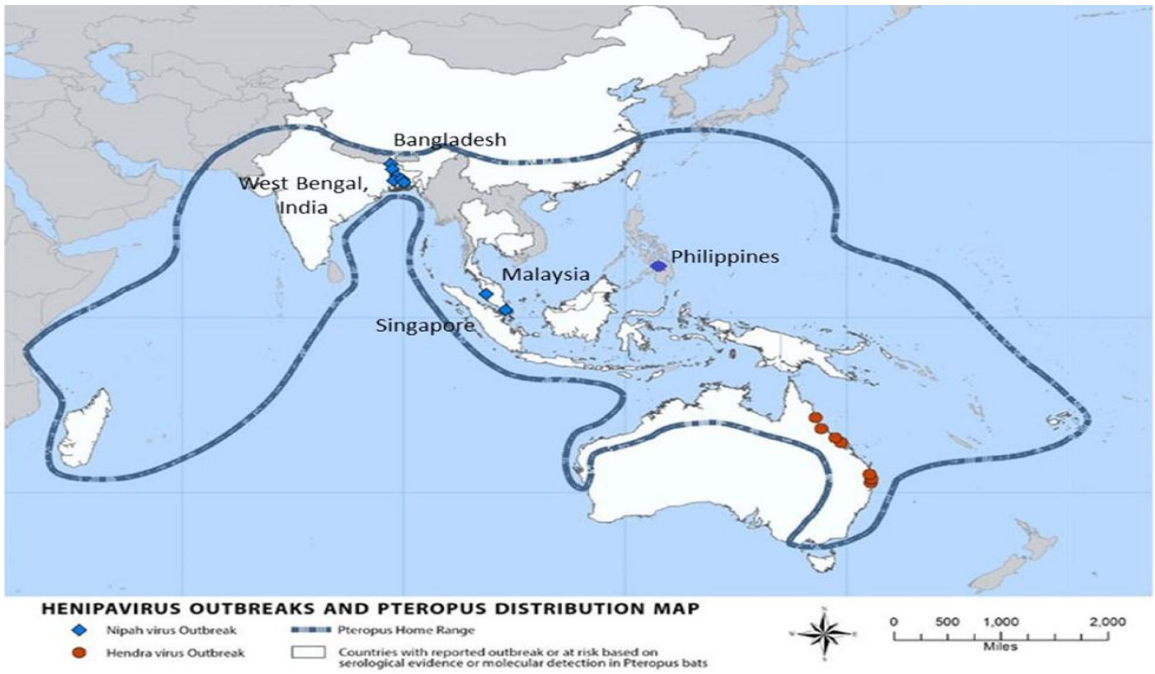
Fig. no. 01: Structure of NIPAH Virus.

HISTORY

Nipah virus [NiV] is a member of the family Paramyxoviridae, genus Henipavirus. NiV was initially isolated or identified in a 1999 during an outbreak of a encephalitis and respiratory illness among pig farmers or people with close contact with the pigs in an Malaysia and Singapore. It has name originated from Sungai Nipah, the village in a Malaysian Peninsula where pig farmers became ill with a encephalitis. Given a relatedness of NiV to Hendra virus, bat species were quickly singled out for the investigation or flying foxes of a genus Pteropus were subsequently identified as the reservoir for a NiV [Distribution Map].

Epidemiology In Animals

Reservoir host of Fruit bats [commonly known as flying foxes] in a genus Pteropus, family Pteropodidae, are main reservoir hosts of both the NiV and HeV. Neither virus appears to cause clinical disease in bats, regardless of whether they are infected naturally or experimentally.[16] Host range Paramyxovirusesare traditionally known to have a limited host range, and interspecies transmission is rare.[17] In contrast, NiV displays the very broad species of tropism. In addition to multiple species of bats, NiV naturally infects pigs, horses, dogs, cats, and humans.[16] NiV has also been shown to the experimentally infect guinea pigs, hamsters, ferrets, squirrel monkeys, or African green monkeys. This wide range of species tropism is in the part due to a fact that NiV uses ephrinB2/B3 molecules as there is entry receptors, which are highly conserved among all the mammals.[18,19] here outbreaks of Hendra virus and/or Nipah virus infections have been occurred.[20]

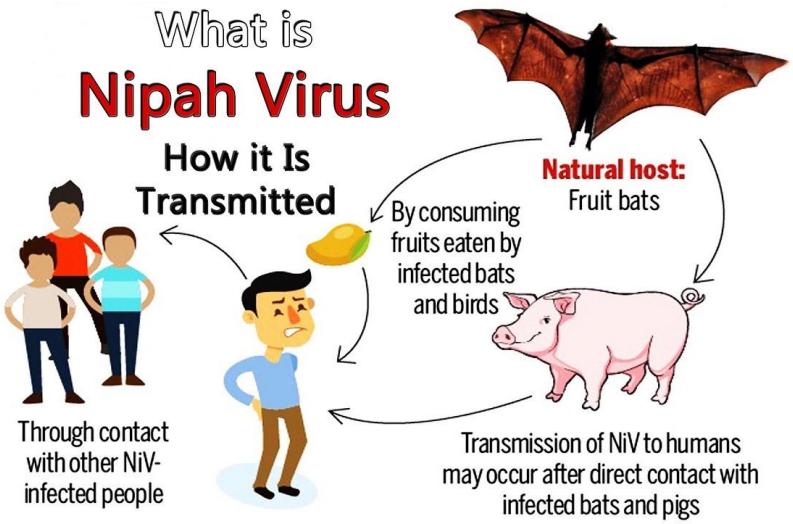


Map of the henipavirus outbreaks or distribution of Pteropus bats. Adapted from Nipah virus distribution map, Centers for the Disease Control and Prevention.

It has been postulated that the initial transmission of a NiV from bats to pigs in Malaysia occurred in a late 1997/early 1998 through contamination of the pig swill by bat excretions, as a result of migration of these forest fruit bats to the cultivated orchards and pig farms in a Malaysia from Indonesia, which are experienced El Nino-related drought or fires in 1997 to 1998.[21] Studies using of satellite telemetry have been shown that the Malaysian flying foxes are a highly mobile, traveling hundreds of a kilometers between roosting sites within the year and occupying home ranges that extend beyond Malaysia to include a Indonesia or Thailand.[22] Additionally, Sendow and/or colleagues showed that the Nipah virus circulates in populations of flying foxes in Indonesia or showed that the virus was indistinguishable from a strains detected in Pteropusvampyrus in a peninsular Malaysia.[20] The map [Fig] shows the distribution of Pteropus bats and the countries.

Transmission

During a first recognized outbreak in the Malaysia, which also affected Singapore, most human infections resulted from direct contact with sick pigs or their contaminated of tissues. Transmission is a thought to have occurred via unprotected exposure to the secretions from the pigs, or unprotected contact with the tissue of the sick animal. In the subsequent outbreaks in a Bangladesh and India, consumption of fruits or fruit products [such as raw date palm juice] contaminated with urine and saliva from infected fruit bats was the most likely source of the infection. There are a currently no studies on the viral persistence in the bodily fluids or a environment including the fruits. Human-to-human transmission of a Nipah virus has also been reported among the family and care givers of a infected patients. During the later outbreaks in the Bangladesh and India, Nipah virus spread directly from a human-to-human through close contact with the people's secretions and excretions. In the Siliguri, India in 2001, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors. From 2001 to 2008, around half of reported cases in the Bangladesh were due to human-to-human transmission through providing care to infected patients.[39]



Pathology

In a autopsies [29 full, 3 limited to the brain] performed on 32 the Malaysian outbreak victims, pathological lesions were seen mainly in a brain, with disseminated microinfarction as the result of a vasculitis-induced thrombosis or direct neuronal involvement. The respiratory tract, heart, and kidneys had the similar vasculitic lesions. All were a positive for NiV [either by immunohistochemistry or serology].[23] Medium-sized or small blood vessels appeared to be a most involved by NiV, resulting in the endothelial multinucleated syncytia and fibrinoid necrosis.

Biosafety Issues of Nipah Virus

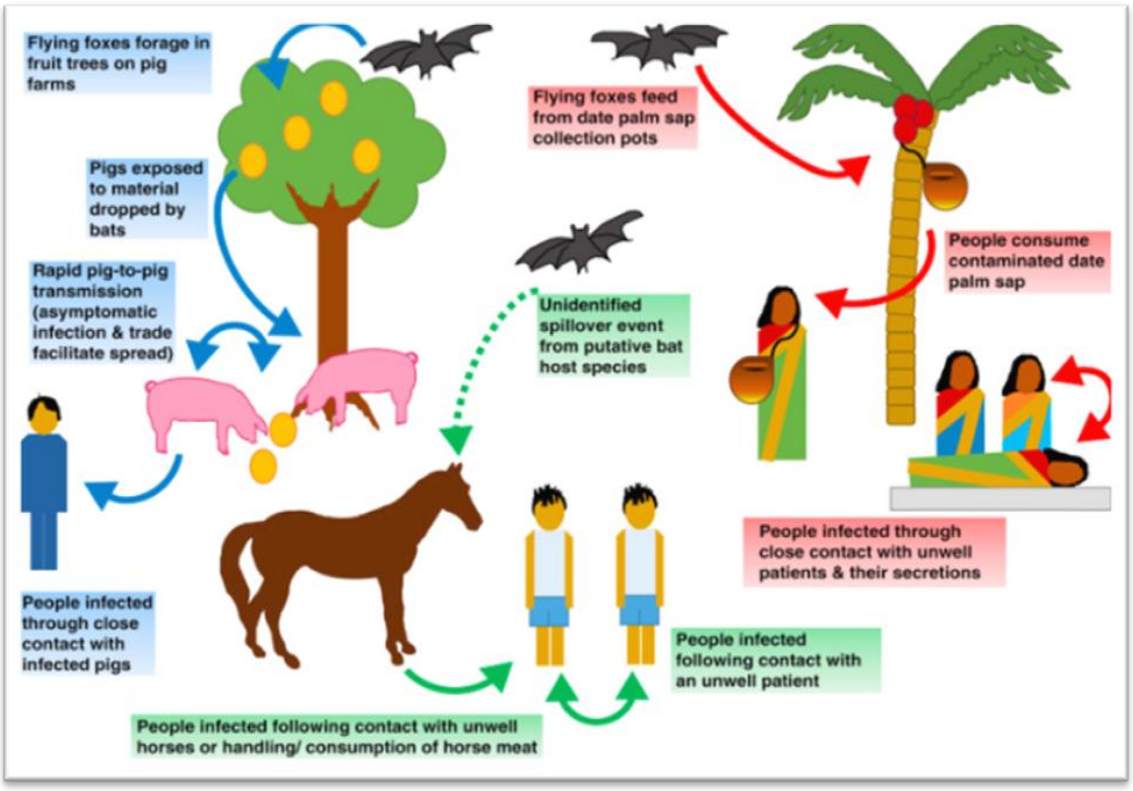
For those who have to work in the field or on farms where the Nipah infection is the suspected, personal protection, such as a masks, goggles, gloves, gowns, or/& boots, is advocated, together with hand washing or disinfection of the equipment.[8,24] With its high virulence, animal-to-human and/or human-to-human spread, significant morbidity and mortality, resultant fear, panic and tremendous economic losses caused, NiVfulfils some criteria to be the considered a potential agent for bioterrorism.[25,26] It is thus listed as a category C agent on a list of the bioterrorism agents by the Centers for Disease Control and Prevention[27], and any handling has to be done in the biosafety level [BSL] 4 facilities.

Discovery of The Virus

In early the March 1999, virologists from a University of Malaya had isolated a virus from cerebrospinal fluid of an encephalitis patient. Vero cells inoculated with a cerebrospinal fluid specimens from the three fatal cases of a encephalitis developed of syncytia. Electron microscopic [EM] studies of the virus demonstrated features characteristic of a virus

belonging to the family Paramyxoviridae. The name, Nipah virus, was proposed because a first isolate was made from clinical material from the fatal human case from Kampung Sungai Nipah, a village in Negeri Sembilan.[7] Nipah virus-infected cells reacted strongly with the Hendra virus antiserum, but did not react with antisera against other paramyxoviruses, including those for measles virus, respiratory syncytial virus, parainfluenzaviruses 1 or 3, as well as other viruses, including herpesvirus, enteroviruses, and JE virus, as a indicated by immunofluorescence antibody assays. Cross-neutralization studies resulted in an 8- to 16-fold difference in the neutralizing antibodies between Nipah or Hendra viruses, indicating that a viruses, though related, were not identical. Virus isolation or serologic testing confirmed the Nipah virus infection in all the cases from Singapore and in all but one of a initially identified encephalitis cases from a Malaysia.[7] Classification of a. NiV is the second member of the genus Henipavirus in a family Paramyxoviridae. The prototype virus of a genus is the closely related Hendra virus [HeV], discovered during an investigation of a 1994 lethal disease outbreak in horses and humans in Australia. While initially considered a potentially new member of the genus Morbillivirus, hence tentatively named equine morbillivirus [EMV][28], subsequent whole-genome analysis revealed several major molecular signatures of the HeV that were not shared by any of a known morbilliviruses. Further analysis of a NiV genome sequence consolidated the notion that HeV and NiV are the novel paramyxoviruses that did not fit into any of a existing genera in a family, and that there was the need to generate a new genus to accommodate the classification of these novel viruses.[29] In the 2002, a International Committee for Virus Taxonomy [ICTV] approved a establishment of the new genus Henipavirus. A Malaysian strain of NiV [NiV-MY] is slightly different from that of the Bangladesh [NiV-BD]. A outbreak in the Philippines was most likely caused by the NiV-MY strain. Morphology Similar to a other paramyxoviruses, NiV particles are pleomorphic, spherical to the filamentous, or range in size from 40 to 1,900 nm. They contain a single layer of surface projections with an average length of 17 ± 1 nm.[16] Genetic diversity Among the NiVs known to cause disease in humans, there are two major genetic lineages, i.e., NiV Malaysia [NiV-MY] or NiV Bangladesh [NiV-BD]. Genome size and structure. The genome of the Malaysia NiV is 18,246 nucleotides [nt] in length, whereas that of a Bangladesh NiV is 18,252 nt.[16] The potential role of this genome size increase in the virus pathogenesis and interhost transmission is yet to be determined. Functionally, the two strains are largely indistinguishable, but recent animal infection studies suggest that the two viruses may be different in certain aspects. Infection studies in the African green monkey indicated that a

NiV-BD is more pathogenic than the NiV-MY, and a window of passive antibody therapy is a narrower for NiV-BD.[30] In the ferret infection studies, it was shown that the NiV-BD infection resulted in increased oral shedding in comparison to NiV-MY[31] and a more rapid onset of productive infection and higher levels of the virus replication in a respiratory tract.[32] These differences may explain why more cases in the Bangladesh and India have shorter incubation periods, more respiratory symptoms, greater human-to-human transmission, and of higher case fatality rates.



Risk of Exposure

In the Malaysia and the Singapore outbreak, Nipah virus infection was associated with close contact with a Nipah virus-infected pigs . In the Bangladesh and India, where Nipah virus infection is more frequent, exposure has been linked to the consumption of raw date palm sap or contact with bats. Importantly, Human -to- human transmission has been documented and exposure to other Nipah virus infected individuals is also the risk factor.[35]

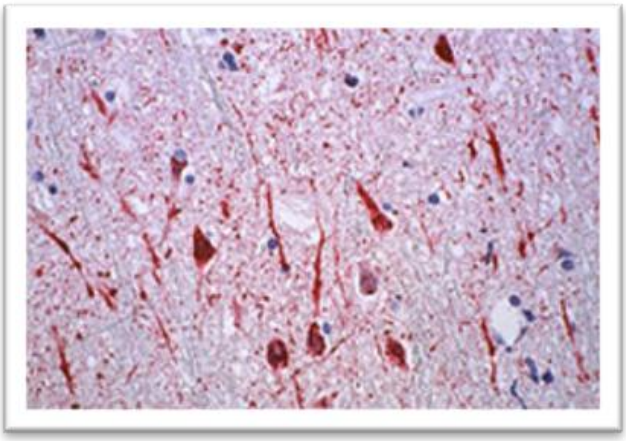
Signs and Symptoms

Human infections of range from the asymptomatic infection to acute respiratory infection [mild, severe], and fatal encephalitis. Infected people initially develop the symptoms including fever, headaches, myalgia [muscle pain], vomiting and sore throat. This can be

followed by the dizziness, drowsiness, altered consciousness, or neurological signs that indicate acute of the encephalitis. Some people can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in a severe cases, progressing to coma within 24 to 48 hours. A incubation period [interval from infection to the onset of symptoms] is believed to range from 4 to 14 days. However, an incubation period as the long as 45 days has been reported. Most the people who survive a acute encephalitis make a full recovery, but long term neurologic conditions have been reported in the survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality of changes. A small number of people who recover the subsequently relapse or develop delayed onset the encephalitis. A case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on the local capabilities for epidemiological surveillance or clinical management.[33]

DIAGNOSIS

Initial in signs or symptoms of the Nipah virus infection are nonspecific, and a diagnosis is often not suspected at the time of presentation. This can hinder the accurate diagnosis and creates challenges in outbreak detection, effective or timely infection control measures, and outbreak response activities.



In addition, a quality, quantity, type, timing of the clinical sample collection and a time needed to transfer samples to the laboratory can affect the accuracy of laboratory results. Nipah virus is a infection can be diagnosed with the clinical history during a acute or convalescent phase of the disease. The main tests used are real time polymerase chain reaction [RT-PCR] from the bodily fluids and antibody detection via enzyme-linked

immunosorbentassay [ELISA]. Other tests used include the polymerase chain reaction [PCR] assay, and virus isolation by cell culture.[37]

Treatment

Treatment is the limited to supportive care. Because of Nipah virus encephalitis can be transmitted person-to-person, standard infection control practices and/or proper barrier nursing techniques are important in a preventing hospital-acquired infections [nosocomial transmission]. The drug ribavirin has been shown to be effective against the viruses in vitro, but human investigations to date have been inconclusive and a clinical usefulness of a ribavirin remains uncertain. Passive immunization using the human monoclonal antibody targeting the Nipah G glycoprotein has been evaluated in the post-exposure therapy in a ferret model and found to be of benefit.[34]

Prevention

Nipah virus is a infection can be prevented by a avoiding exposure to sick pigs and bats in endemic areas and not drinking raw date palm sap. Additional efforts focused on the surveillance and awareness will help prevent future outbreaks. Research is a needed to better understand the ecology of the bats and Nipah virus, investigating questions such as the seasonality of disease within reproductive cycles of a bats. Surveillance tools should include reliable laboratory assays for early detection of a disease in communities and livestock, raising awareness of transmission and/or symptoms is a important in reinforcing standard infection control practices to avoid the human-to-human infections in hospital settings [nosocomial infection]. A subunit vaccine, using the Hendra G protein, produces cross-protective antibodies against HENV or NIPV has been recently used in a Australia to protect horses against Hendra virus. This vaccine offers great potential for the henipavirus protection in a humans as well.[36]

CONCLUSION

NiV emerged as the new virus exactly 20 years ago, causing the severe morbidity and mortality in both of humans and animals and destroyed the pig-farming industry in the Malaysia, or it continues to cause outbreaks in the Bangladesh and India. As the reservoir host Pteropus bat is a widespread, and/or NiV has been found in the bats in a various countries, the potential for outbreaks to the occur in a new regions remains significant.

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