

Potential pandemic pathogens series: Nipah virus

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In the last two years we have experienced the effects of the COVID-19 pandemic in our lives and hospitals. Pandemics are part of the history of humanity and we can be certain that in the future new pandemics will appear. In fact, due to the growth in the human population, increased travel and global warming, it is to be expected that new pandemic pathogens will arise more frequently than before. Additionally, decreased barriers between animals and humans will give rise to spillover events which may result in the introduction of new zoonotic pathogens in humans. In each of the parts of this series we will, in a short format, highlight a potential pandemic pathogen and describe its characteristics, history and potential for global pandemics. In this part of the series we focus on the Nipah virus. Nipah virus is currently on the WHO's list of global priority pathogens as it possesses pandemic properties, is highly infectious and potentially fatal. Here we explore the past, present and future of Nipah virus.

Introduction

In September 1998, a novel and fatal viral infection was discovered near Ipoh city by the Nipah river in Malaysia.^[1] The first outbreak occurred mainly among adults working in close contact with pigs. Initially the infection spread among pigs that developed fever and predominantly respiratory symptoms. As the animals started to die, pig farmers became ill as well. The clinical picture in humans was somewhat different than in pigs as humans mainly developed neurological symptoms consistent with encephalitis.^[2] The infection was initially mistaken for Japanese encephalitis virus due to its overlapping geographic location and encephalitic nature.^[3] However, Japanese encephalitis is spread by mosquitos and thus not necessarily associated with occupation. Furthermore, Japanese encephalitis mainly affects children and in this outbreak mostly adult pig

farmers were infected. Another sign that another virus could be responsible for the outbreak is that although pigs serve as amplifying hosts for Japanese encephalitis, they are usually asymptomatic when infected.^[2] Measures were taken to reduce mosquito populations by spraying, and immunising workers with a Japanese encephalitis vaccine. Neither measure slowed the epidemic.

In a frantic attempt to contain the virus, 890,000 pigs were culled by the Malaysian government in the span of several months.^[2] Nevertheless, the virus continued to spread in close proximity to the infected pigs: next up was the southern state of Negri Sembilan which served as a platform for its spread to Singapore where infected pigs were transported to. Given the doubts whether Japanese encephalitis was the causative agent, the virus was isolated and transported to the CDC. Investigations there showed that indeed a novel virus was involved since electron microscopy identified the presence of a paramyxovirus. Years before, in 1994, another paramyxovirus, Hendra virus, caused a large outbreak in Australian horses and their handlers but studies showed that this was a new Hendra-like virus, which was subsequently named after Nipah, the town where it first arose. Nipah virus (NiV) was identified in 1999 as an RNA virus belonging to the *Paramyxoviridae* family, genus *Henipavirus*.^[4] Sequencing the viral genome revealed that NiV was merely 20% different from the Hendra virus, whose natural hosts are Pteropodid fruit bats.^[4] Later it was identified that the NiV had spilled over to animals from its natural reservoir, the fruit bat. Deforestation and the habit of housing pigs in areas where a lot of fruit trees were present had led to a closer proximity of fruit bats and pigs, who became infected after coming in contact with urine or faeces of bats or after eating fruit that had also been touched by bats. Transmission of the virus occurs horizontally via urine, faeces and saliva, not only to pigs but onto a wide range of hosts such as cats, dogs, horses and humans.^[5] A schematic representation of infection routes for NiV is shown in *figure 1*.

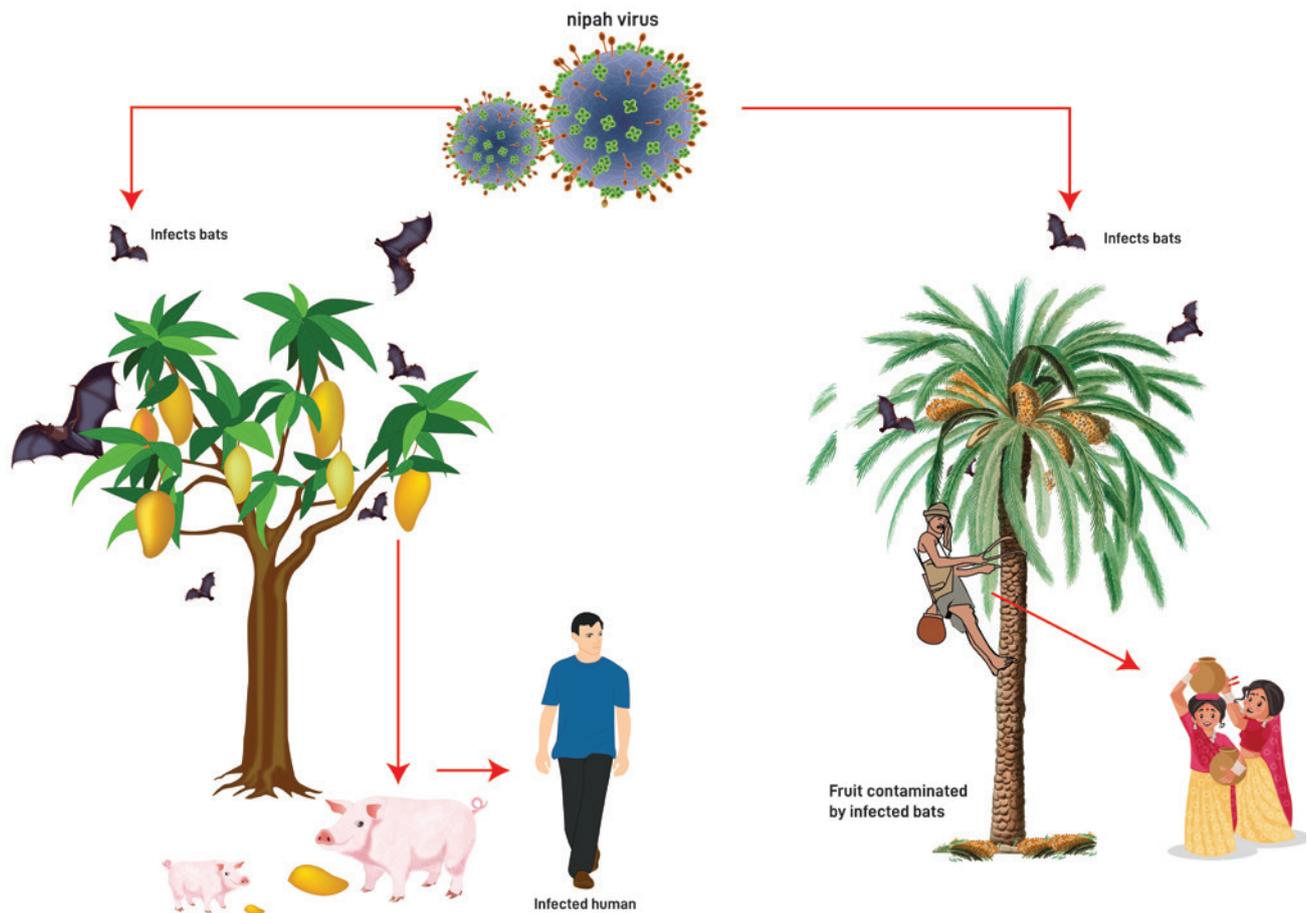


Figure 1. Infectious routes of Nipah virus. The fruit bat is the vector of Nipah virus, infection may occur through infected pigs or through direct consumption of contaminated fruit or date palm sap.

Although no new cases were reported after pig importation to Singapore ceased, it has since resurfaced multiple times in southeast Asia with staggering mortality rates.^[3] The outbreak in Malaysia ended when 1.1 million pigs were culled, and disease in Singapore stopped when importation of pigs from Malaysia was halted. A total of 283 human cases with 109 fatalities (39% fatality) were recorded.

Clinical presentation

The incubation period in 90% of humans is 4-14 days, although incubation periods of 45 days have been reported.^[6] Upon entry, NiV damages various endothelial cells such as those of the gastrointestinal, pulmonary and central nervous system allowing its spread to the body.^[7] By damaging endothelial cells NiV not only passes selective borders such as the blood-brain barrier but consequentially can cause systemic vasculitis, thrombosis and necrosis.^[7] Infection can be asymptomatic or present with symptoms ranging from fever, pneumonia, vomiting, headache and seizures, to symptoms consistent with severe encephalitis

that may progress to coma.^[6] The fatality rate generally varies from 50-75% depending on clinical management,^[6] but rates of up to 95% have been reported.^[3]

Diagnosis, prevention and treatment

Primary diagnosis mainly occurs via real-time PCR (RT-PCR) from respiratory secretions, urine or cerebrospinal fluid, as it is highly sensitive (close to 1 plaque-forming unit) and specific; although percentages of sensitivity and specificity are high, they vary with the actual PCR which is used. PCR for NiV is currently only available at the Erasmus Medical Center. Further options include immunohistochemistry, virus isolation and antibody detection (Elisa, serum neutralisation test).^[3]

Given its horizontal transmission, efforts towards preventing the spread of NiV have centred around increasing awareness about the dangers of consuming contaminated foods, such as raw date palm sap which is contaminated by bats licking date palm's sap producing surface or bat excreta (*figure 1*).^[8]

Once a host, such as a farm animal, is infected personal protective clothing such as gloves, a cover for the mouth and nose, goggles and long protective clothing should be worn while handling the sick animal. Person-to-person transmission is additionally reduced by isolation; thorough testing of contacts is performed and they are kept under observation until they test negative.^[3] Due to the fact that human contact is the highest risk factor for transmission, extra caution and protection should be taken when treating patients.^[9]

Treatment is mostly supportive and symptomatic. There is no confirmed specific treatment for NiV in humans aside from fluid and electrolyte maintenance as well as monitoring of vital signs. In severe cases mechanical ventilation following standard mechanical ventilation guidelines and/or anticonvulsant therapy may be required.^[10] Currently, there are no vaccines that specifically target NiV in humans; however, promising vaccines have shown to be effective in animal models, including non-human primates, on a small scale. Complete protection has been achieved against oro-nasal NiV challenge in these models after a single dose.^[11-13]

Pandemic potential of Nipah virus

After emerging in Malaysia in 1998 and spreading to Singapore in 1999, NiV has successfully been brought to a halt in these countries after culling thousands of pigs, as no new cases have been reported since the initial outbreak.^[7] However, Bangladesh, the Philippines and India have witnessed outbreaks of NiV, in some cases seasonally. In *figure 2* a map is shown depicting the world-wide distribution of NiV outbreaks as well as reported sites where fruit bats have tested positive for NiV. Bangladesh has had seasonal outbreaks since 2001, resulting in a total of 319 confirmed cases coinciding with the date palm sap harvesting season.^[8] The majority of these cases occurred in- but were not limited to- a region known as the Nipah belt which stretches along the border with India.^[14] The Philippines experienced a fatal outbreak in 2014 with 17 confirmed cases and a fatality rate of 82% in those with acute encephalitic syndrome. Five patients acquired NiV through person-to-person transmission by a strain that was closely related to the Malaysian strain where person-to-person transmission had not been identified,^[15] suggesting quick viral mutation in the span of several years.

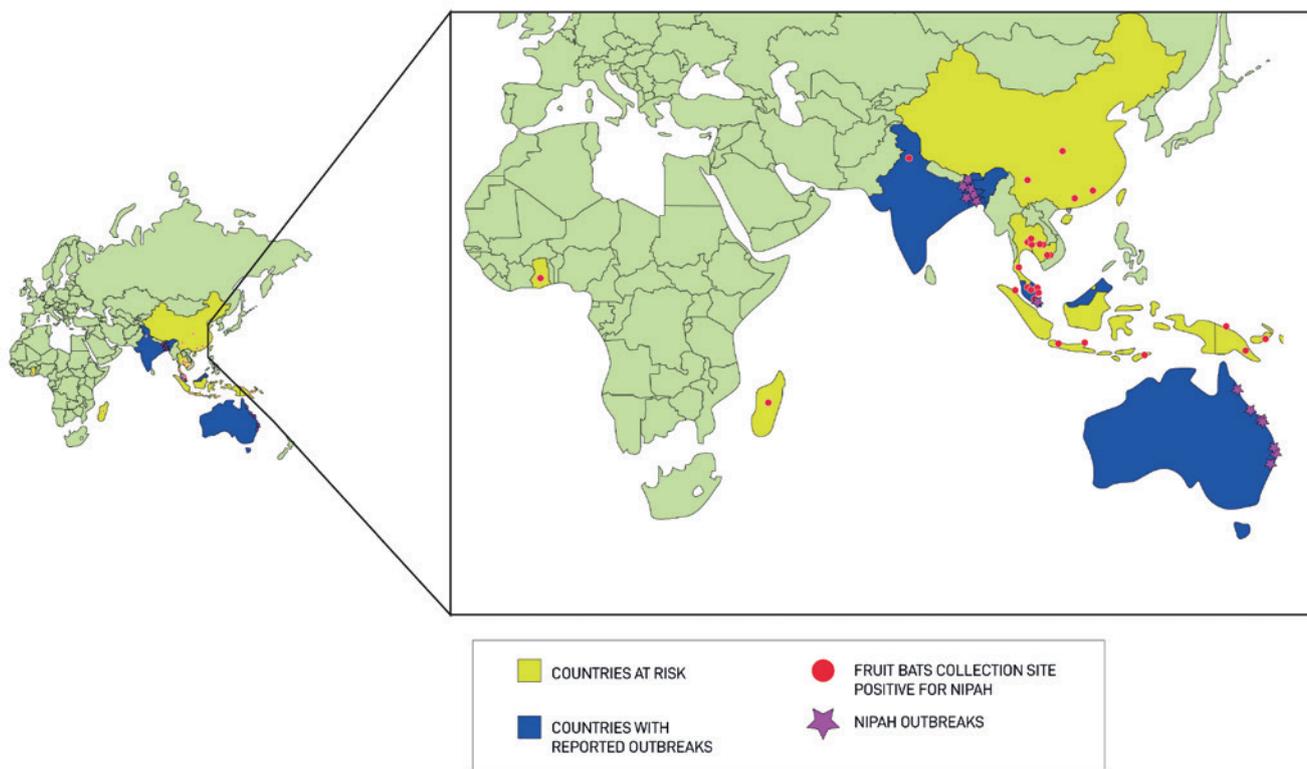


Figure 2. Worldwide distribution of countries at risk and those with reported outbreaks as well as the locations of Nipah outbreaks and sites where fruit bats tested positive for Nipah virus

Three NiV outbreaks have been reported in India, two of which were across the Nipah belt in Bangladesh.^[3] The third outbreak occurred in 2018 in the Kozhikode and Malappuram districts of Kerala, which is a southern state geographically disconnected from previous outbreak regions. Of 18 confirmed cases, 17 died as a result of NiV.^[3] Being one of the most densely populated regions on earth, inhabitants of southeast Asia such as Bangladesh are not only in close proximity to one another, thus allowing person-to-person spread, but are also rapidly deforesting in order to create new living space. By doing so, fruit bats which typically reside in dense forests are forced to co-exist with humans and other hosts, thus increasing the risk of spillover.^[16]

RNA viruses are infamous for their exceptionally high rate of mutation,^[17] further demonstrated by the fact that only one single strain was detected in Malaysia whereas several years later a substantial genetic heterogeneity was observed in Bangladesh.^[18] Additionally, incubation periods of up to 45 days have been reported allowing the fatal virus to spread unnoticed.^[6] A contributing factor may also be the socioeconomics of a country such as Bangladesh where the illiteracy rate remains high and prevention of consuming possibly contaminated fruits or raw date palm sap has been shown to be difficult.

Conclusion

Nipah virus is a lethal RNA virus which is currently on and off endemic to southeast Asia. The virus is horizontally transmitted from its natural reservoir, the Pteropodid fruit bat. After infection, humans show a variety of symptoms though most commonly of a neurological nature with the potential to progress to coma.

After its first known outbreak in Malaysia in 1998, it has resurfaced seasonally in southeast Asia. Although the number of infected people, as yet, is not staggering, it must be monitored given its lethal nature, mutation rate and geographic spread. The WHO considers NiV one of nine priority pathogens for research and development in emergency contexts for which the development of adequate treatment or vaccination is urgently warranted.

Disclosures

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