What you need to know about Nipah virus

April 20 2023, by Priya Dhagat and Rodney E. Rohde

Preliminary data suggest that bats of the genus Pteropus are the reservoirs for Nipah virus in Malaysia. Credit: Brian W.J. Mahy/CDC Public Health Image Library

A mysterious illness causing fevers and headaches and leading to rapid development of acute encephalitis (within a couple of weeks of symptom onset), caused an outbreak of nearly 300 reported cases and over 100

fatalities in Malaysia and Singapore between September 1998-May 1999. Over 90% of these cases originated from contact with sick pigs.

Central nervous system tissue cultures from deceased individuals identified a previously unknown infectious agent. Electron microscopy demonstrated structures consistent with a paramyxovirus, and immunofluorescence tests suggested a virus related to Hendra virus—a member of the family Paramyxoviridae, now housed in the genus named Henipavirus. The causative agent was later named Nipah virus (NiV), after the Malaysian village of Kampung Sungai Nipah.

How is Nipah virus transmitted?

Fruit bats, also known as flying foxes, are the natural reservoir hosts of NiV. The virus is present in bat urine, feces and saliva. Fruit trees can attract bats from surrounding habitats. Bats inhabiting the fruit trees lead to spillover through contamination of farms, soil or fruit.

Since NiV can survive in substances that are rich in sugar, such as in fruit pulp or date palm sap, consumption of contaminated fruit can lead to infection. In the 1998 outbreak in Malaysia, fruits that were partially consumed by bats infected with the virus were subsequently ingested by pigs. Then workers and pig farmers became infected after close contact with ill pigs.

Past and present Nipah outbreaks

Several countries have reported NiV outbreaks, including Bangladesh, India, Philippines, Malaysia and Singapore. In India, outbreaks have been reported in the states of West Bengal (2001 and 2007) and Kerala (2018 and 2021).

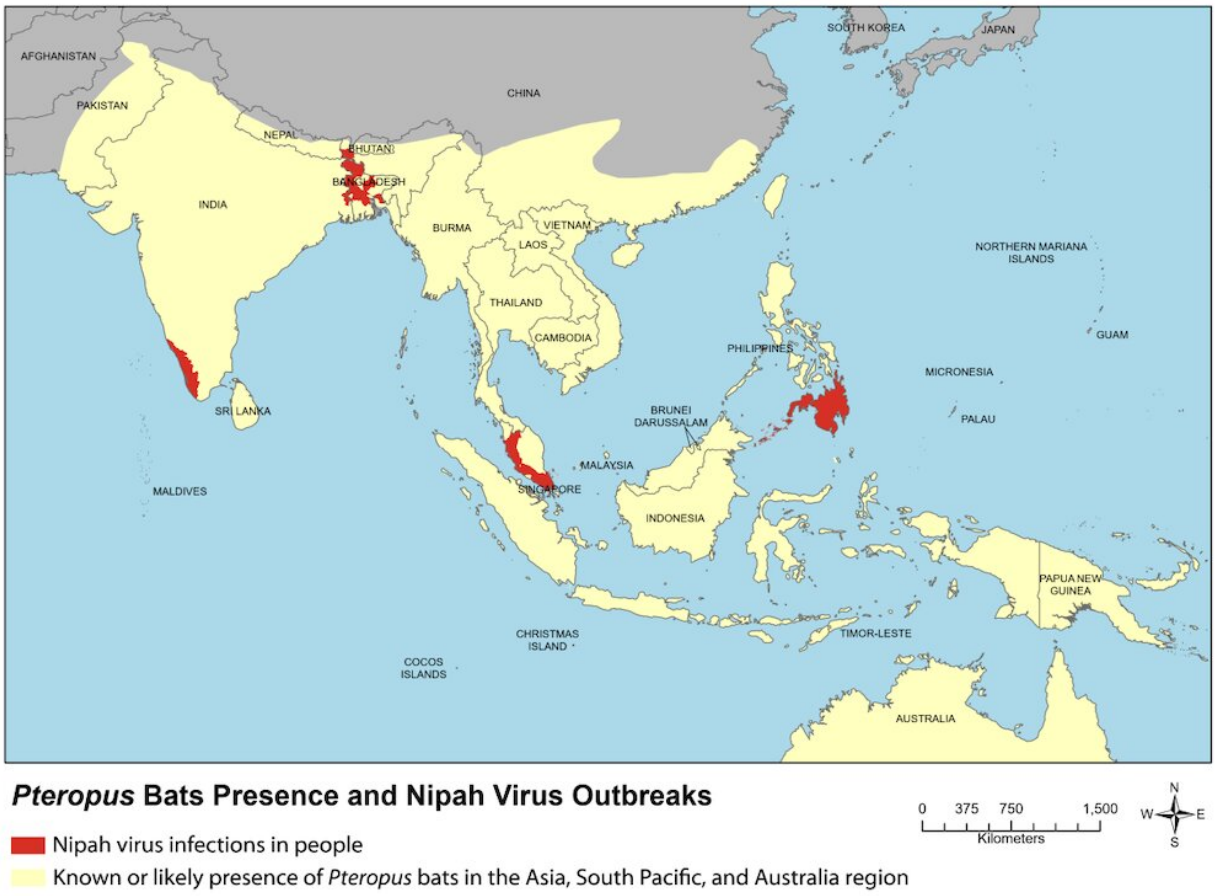
In 2014, a Nipah outbreak in Singapore involved 17 cases between

March and May. This outbreak was linked back to exposure to infected horses and contact with contaminated body fluids from sick horses during slaughtering and/or consumption of contaminated or undercooked horse meat. Secondary human-to-human cases likely occurred due to lack of appropriate preventative measures and infection control practices in the homes of infected individuals and in healthcare facilities.

A few years later, a Nipah outbreak struck Kerala, India in 2018 and involved 13 cases with 11 deaths. Evidence suggests that the likely origin of this outbreak was exposure to bat secretions from forest trekking, eating fruits bitten by bats or exposure to bats and their secretions contaminating an unused well.

In Bangladesh, human consumption of raw date palm sap contaminated with NiV from bat excretions is a major risk factor for acquiring NiV infection and has led to recurring outbreaks. These outbreaks often follow a seasonal pattern in the winter and spring seasons (November to April), which coincides with date palm sap harvest.

According to a March 2023 report from the World Health Organization (WHO) and the Bangladesh Institute of Epidemiology, Disease Control and Research (IEDCR), the current 2023 outbreak has accumulated 14 cases and claimed 10 lives. Cases have been reported across seven districts in Bangladesh thus far, although, historically, cases have been reported in numerous districts across the country.



Countries with previously reported outbreaks of Nipah virus in people (yellow). Countries where Pteropus bat species are known or likely present (red). Source: CDC

Pathogenesis and diagnosis

NiV is a single-stranded, non-segmented, enveloped RNA virus. The RNA genome consists of 6 genes: nucleocapsid (N), phosphoprotein (P), matrix (M), fusion glycoprotein (F), attachment glycoprotein (G) and long polymerase (L). The F and G proteins are responsible for cellular attachment and entry into the host cell. The virus infects respiratory epithelial and pulmonary endothelial cells, and eventually enters the

bloodstream, where it infects organs, including the spleen, kidney and brain. Viral entry into the central nervous system damages the blood-brain barrier, leading to neurological symptoms. Symptoms of NiV infection include fever, headaches, myalgia, respiratory illness, seizures, blurred vision and encephalitis.

NiV symptoms typically appear in 4-14 days following exposure to the virus. Encephalitis (brain swelling) may follow early symptoms, leading to drowsiness, disorientation and mental confusion, which can rapidly progress to coma within 24-48 hours. Mortality occurs in 40-75%. Long-term side effects in survivors of NiV infection include persistent convulsions and personality changes. Interestingly, dormant or latent infections, leading to symptoms or death, have also been reported months and even years after exposure.

Diagnosis of NiV infection is possible during illness or after recovery with a variety of medical laboratory tests. Laboratory testing in early-stage infection can be performed with real-time polymerase chain reaction (RT-PCR) from throat and nasal swabs, cerebrospinal fluid, urine and blood. At the end of illness, and after recovery, indirect testing for antibodies against NiV can be performed using an enzyme-linked immunosorbent assay (ELISA).

Defining an algorithm for early diagnosis of NiV infection is challenging due to the non-specific early symptoms of the illness noted prior. One consideration should be for individuals with symptoms consistent with NiV infection (e.g., fever, headache, cough, sore throat and other respiratory difficulty) who have been in areas where Nipah virus is more common, such as Bangladesh or India—particularly if they have a known exposure. Early detection and diagnosis increase survival among infected individuals and assist with prevention of transmission and outbreak management.

Treatment and vaccine candidates

Currently, there are no licensed treatments for NiV. Individuals with NiV infections are limited to supportive care, including treatment of symptoms. Immunotherapeutic treatments (monoclonal antibody therapies) are currently under development and evaluation for treatment of NiV infections. Monoclonal antibody, m102.4, has completed phase 1 clinical trials and has been administered on a compassionate-use basis. In addition, the antiviral treatment remdesivir has been effective in nonhuman primates when given as post-exposure prophylaxis. Ribavarin efficacy for NiV is unclear but was used to treat a small number of patients in the initial Malaysian NiV outbreak.

Currently, there are no licensed vaccines in the United States for Nipah virus, though research to develop a NiV vaccine is ongoing. In July of 2022, the National Institutes of Health (NIH) reported an early-stage clinical trial for an investigational Nipah vaccine based on a messenger RNA (mRNA) platform developed by Moderna, Inc., Cambridge, Massachusetts. Results of this trial will be expected after the trial is completed; none are yet available.

In December of 2022, a *Lancet* publication reported that a VSV-EBOV vaccine expressing NiV glycoprotein G (VSV-NiVG) induced high neutralizing antibody titers and afforded complete protection from homologous and heterologous challenge with Nipah virus Bangladesh and Nipah virus Malaysia genotypes, respectively, in the African green monkey model. This was a promising step in the pursuit of a vaccine that confers broad protection against NiV.

One Health approach

After NiV first emerged in pigs in Malaysia in 1998, pig-to-human (zoonotic) transmission, associated with severe febrile encephalitis, was

described. These reports led to the hypothesis that NiV transmission occurred through close contact with infected animals. Although the first outbreaks did not identify an intermediate animal host, most recent reports suggest bat-to-human and human-to-human.

Identifying how new viruses emerge in naïve populations and pinpointing source identification is important to understand the epidemiology of any disease; however, this is extremely challenging. To understand NiV, it is important to identify and document the spillover event between species and to characterize how bats move over trans-natural boundaries (border between two or more countries or areas and affecting both or all areas, including water like rivers, etc). NiV has certainly shown that it can move beyond one host species and infect others— including humans. Nipah research therefore requires a "One Health approach," in which multiple sectors coordinate and work together to achieve better public health outcomes. It is imperative that the global public health, research and healthcare community work together in an interdisciplinary effort at all levels and across political and geospatial lines to prevent further Nipah virus transmission.

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