



Update on the Nipah Virus Outbreak in Kerala, India

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What is Nipah virus and why should we be concerned about the Nipah virus outbreak?

- Nipah virus was first detected during a major infectious disease outbreak in Malaysia in 1998-9 and the virus was named after the Sungai Nipah village on the banks of Nipah River in Malaysia.
- Nipah virus belongs to a genus of paramyxoviruses (*Henipavirus*), including the highly pathogenic Hendra virus found in Australia that can cause acute respiratory distress and encephalitis with mortality rates in excess of 70%.
- Since its first detection in Malaysia, a closely related Nipah virus has emerged in Bangladesh/India region since 2001. The Nipah Bangladesh strain (Nipah virus-BD) is approximately 91% identical in genome sequence to the Nipah Malaysia strain (Nipah virus-MY).
- In 2015, there was a Nipah virus outbreak in the Philippines which affected 17 individual with a case mortality reaching 80% for those developing neurological symptoms. Preliminary serological and molecular data indicated it was caused by the Nipah virus-MY strain or a closely related virus.
- Pteropus bats (fruit eating bats) are likely the main animal reservoir for Nipah virus, although there is evidence suggesting that other bat species are also susceptible to Nipah virus infection in nature. Various bat species ranging from Australia to West Africa can carry viruses genetically closely

related to henipaviruses.

- Studies from the known human infection outbreaks in Australia, Malaysia, Singapore, Bangladesh, India, and the Philippines, show that the virus can be transmitted to human by three different routes: 1) from bats to humans who come in contact with virus-contaminated material (e.g., date palm sap); 2) from intermediate hosts such as pigs and horses; and 3) from infected humans.
- There is also epidemiological evidence that companion animals (including dogs and cats) can be infected with these viruses and they can in theory transmit viruses to humans as well.

What do we know about the Kerala outbreak?

- The current Nipah virus outbreak in Kerala was first alerted when three members of a family, two brothers (age 26 and 28) and their aunt (age 50), died on May 5th, May 18th, and May 19th, respectively, in the private Baby Memorial Hospital (Kozhikode district, Kerala). They died with signs of viral encephalitis. Laboratory testing was initially conducted at the Manipal Centre for Viral Research using blood and fluid samples from this patient. The etiologic cause of their death due to Nipah virus encephalitis was confirmed by the National Institute of Virology in Pune.
- The father of the two siblings died on May 24 after fighting for his life for about three weeks. In total, four family members died in this “index case” cluster.
- As the incubation period of Nipah virus infection varies from 4 to 14 days¹, it was difficult to definitively determine who was the true “index case” and how was the infection acquired.
- Although more studies are required to prove or disprove that all the human cases are related and resulted from a single spillover event, early genetic analysis seems to indicate that the outbreak was caused by a virus closely related to the Nipah virus-BD strain.
- It is interesting to note that the distance from Kerala to the known “Nipah belt” in western/northwestern Bangladesh and the bordering areas of west Bengal is ~2,600 km (1600 miles).
- As of this writing (Sun May 27), there are 17 confirmed cases with 14 deaths giving a presumptive mortality rate of ~80%. Dozens of samples remain to be tested.
- At least 31 species of bats have been documented in Kerala (including 5

species of fruit bats)² .

- The recent report that 21 samples of bats and pigs from the affected area tested negative for Nipah Virus should be interpreted with caution with regards to expected reservoir.
 - The sample size is too small and the quality of the specimen (especially those from the dead bats in the well near the “index case” cluster) might also be an issue. Contrary to local news reports, it is impossible to rule out bats as a reservoir species based on these 21 samples.
 - As a reservoir species, bats are not supposed to be affected, much less killed by the virus.
 - The bats tested so far are insectivorous bats. A fruit bat colony 4-5 km from the site of the outbreak has yet to be tested.
 - Longitudinal studies of Hendra virus in Australia revealed that the viral load in the bat population could go through short periods of “spikes”. As the timing of the assumed initial spillover event could not be conclusively determined, it is also possible that the viral load in the bat population has dropped recently, hence leading to negative findings.
 - There is a vast literature showing that bats are the natural reservoirs for henipaviruses.

What is the risk of wide spread transmission?

- From past Nipah virus outbreaks, the R_0 was estimated to be ~ 0.4 ³. R_0 is mathematical term quantifying the *average* number of new infections that one infected individual can generate, in an otherwise naïve population. For an infection to spread through a population, R_0 needs to >1 . When R_0 is <1 , the infection will eventually die out.
- Human-to-human transmission requires intimate contact with high levels of bodily secretions (respiratory secretions, saliva, urine, etc.). The risk of wide-spread transmission is therefore low. This is also reflected in estimated $R_0 \sim 0.4$ for Nipah virus.
- The current outbreak appears to be small, and the appropriate public health measures have been rapidly implemented to contain its spread. To put the current Nipah virus outbreak in context, consider the following two vignettes:
 - The 2001 outbreak in Siliguri, India, involved 66 people. The index case transmitted the virus to 11 additional patients at the hospital. These secondarily infected patients were transferred to other

facilities – in two facilities, subsequent transmission involved 25 staff and 8 visitors⁴. This was likely before the implementation of universal precautions— personal protective equipment (PPE) such as gloves, masks and/or face shields.

- 50% of Pteropus bats sampled in an outbreak area (Thakurgaon district) in Northwest Bangladesh were seropositive for Nipah virus antibodies⁵. Yet transmission is still very sporadic. Thus, the drivers of virus spillover remain relatively unknown (other than drinking of virus contaminated date palm sap).

What can we do to contain the outbreak?

- Contact tracing, aggressive monitoring and quarantining of suspect cases are effective forms of infection control and containment. These have been appropriately implemented by the responsible government agencies responding to this outbreak in Kerala.
- Educational efforts combined with preventive measures appear to be effective. Examples include:
 - The use of universal precautions and appropriate PPE (gloves, masks and/or face shield) is sufficient to limit the spread of Nipah virus to patient caretakers including family relatives and healthcare workers.
 - Funeral practices that avoid direct contact with the deceased can cut the train of transmission.
 - Avoiding direct contact with bodily fluids, especially respiratory secretions of infected individuals.
 - Counsel relatives to avoid prolonged close contact with the infected individual (e.g. sleeping beside patient, sharing of foods, etc.).
 - All the above require culturally sensitive educational campaigns targeted to the affected community.
- There is evidence that Nipah virus RNA+ patients are more likely to contaminate towels, bedsheets, and bed rails⁶. A previous study also showed that Nipah virus RNA could also be detected on the surrounding walls and bedframe of a deceased Nipah virus infected patient⁷. Thus, infection controls should target hospital surfaces, which will reduce the risk of fomite transmission.

What's the latest development in diagnosis, treatment and prevention?

- Clinical symptoms include fever and headaches, which can progress to drowsiness, disorientation, mental confusion, and finally encephalitis

(brain swelling) in less than a week.

- Molecular tests (both qPCR and next generation sequencing) are the most rapid and accurate tools available to confirm Nipah virus infection. Acute-phase serum, CSF, throat swabs, saliva, and urine can be used for these tests.
- There is also an IgM ELISA test based on whole viral antigen.
- Live virus isolation should be conducted in a high level biocontainment facility.
- Ribovirin was used during the Nipah virus outbreak in Malaysia, but its effect is non-conclusive. A targeted recombinant human monoclonal antibody therapy has proven to be effective in animal models and has passed Phase I clinical trial. The relevant Indian government agency is in the process of acquiring this therapeutics from the Australian supplier with the help of WHO.
- There are several forms of recombinant vaccines proven to be effective in animal models. These include a recombinant G-protein based vaccine and viral vector-delivered vaccines. The recombinant G-protein vaccine has been licensed for use in horses. With the founding from the Coalition for Pandemics Preparedness Innovations (CEPI), there is an effort to fast track the development of a Nipah virus vaccine for human use.

What is GVN doing for Nipah virus?

- In the past, various GVN members have played a key role in laying the ground work for a good understanding of virology, epidemiology and pathogenesis of Nipah virus.
- GVN member teams are currently helping the Kerala outbreak investigation by providing advices, reagents (when needed), and are ready to deploy field and laboratory experts should the need arise.
- In future, GVN will focus on the following:
 - Better understanding the drivers of spillover events.
 - Identifying and understanding the ecology of its reservoir, so as to guide preventive measures.
 - Identifying potential unknown intermediate/amplifying hosts in different ecological, social, cultural and farming settings.
 - Developing a rapid point-of-care test(s) for deployment in developing nations.
 - Conducting education that is consistent with conservation biology regarding the importance of bats for a healthy ecosystem.

- Stockpiling therapeutics and vaccines which are not economically viable for private companies – CEPI model sets the stage for future proactive response to outbreaks of highly pathogenic emerging viruses.

References

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