

Emergence of Nipah Virus: Need More R&D and Public Health Infrastructure

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An infectious disease outbreak of Nipah virus (NiV) in Kozhikode and Malappuram districts in Kerala (India) has left at least 17 people dead of 18 cases bringing the world's attention in May 2018. The most cases of this outbreak are of family members or health workers caring for individuals. NiV is a zoonotic virus whose natural host is the fruit bat (*Pteropus* bat species) and its outbreak was first reported in 1998-99 when virus moved to pig farmers from pigs in Malaysia and Singapore, infecting 276 and resulting in 106 deaths. Later in 2004 the recurrence of this infection claimed 9 deaths out of 17 reported cases. In India, the NiV infection was first reported in 2001 followed in 2007 claiming 50 lives at the death rate of 70% in both the outbreaks. Annual outbreaks occur in Bangladesh since it was recognized in 2001 through consumption of the contaminated sap of date palm trees by infected bats and there were 199 deaths from 261 cases with case fatality ratio >76% in 2015. A total of six hundred cases have been reported between 1998 and 2015 of NiV infection by WHO in the south and east Asia. There is no specific treatment or vaccine available against NiV infection and only supportive care is offered to affected individuals. The virus has *Pteropus* bats as natural reservoir and other bat species from countries like Indonesia, Philippines, Thailand, Madagascar, Cambodia, and Ghana. While WHO reports the risk of geographical spread of Nipah outbreaks to be low, the wide distribution and extensive migration of fruit bats species raise concerns about the pandemic of NiV with devastating zoonotic potential. Since NiV infection is contagious with a very high mortality rate it is listed as category. A biological warfare agents requiring biosafety laboratories of containment level 4 for handling limiting the interest in NiV research. The high end infrastructure requirement further hinders the research and development in the field of diagnosis and therapeutics in the low income affected countries.

NiV infection primarily is a zoonotic disease (transmitted from animals to humans) and can be transmitted through consuming contaminated food or directly from human to human. Symptoms start after 4-20 days of incubation and illnesses ranges from asymptomatic (subclinical) to and fatal encephalitis. The most common characteristics of NiV infection are high fever, vomiting, and breathing difficulties. The NiV infection even in animals may result in a significant economic loss as seen in Malaysia where 1.1 million pigs were culled in 1998-99.

NiV is a RNA virus that belongs to genus *Henipavirus* of *Paramyxoviridae* family. It is enveloped negative-sense single-stranded RNA virus with a genome size of 18,252

(Bangladesh) and 18,246 (Malaysia) nucleotides. NiV are pleomorphic in nature with size varying from 50 to 150 nm. The genome of NiV is continuous (nonsegmented) and contain six ORFs that codes for structural genes namely, nucleoprotein (N), phosphoprotein (P), matrix protein (M), Fusion protein (F), attachment protein (G) and polymerase or large protein (L) separated by inter-genomic sequences. The genes located at 3' end are transcribed in a greater abundance compared with the genes at 5' end of the genome. RNA polymerase along with phosphoprotein and nucleoprotein forms transcriptase complex that transcribe viral RNA into positive sense mRNA after binding to promoter located at the 3' end and translated into structural and non-structural proteins.

Initial symptoms of NiV infection are nonspecific that affects outbreak response activities like outbreak detection, effective and control measures. The main tests used are IgM and IgG detection by enzyme-linked immunosorbent assay (ELISA), real-time polymerase chain reaction (RT-PCR) from bodily fluids like respiratory secretion, urine, CSF etc., and virus isolation using Vero cells. Immunohistochemistry is also performed in the autopsy cases. As there is no specific treatment available for NiV infection the patients are administered with broad-spectrum antiviral Ribavirin and anticonvulsants. Cases with difficulty in breathing require mechanical ventilation. Equivac® HeV-zoetis developed by Uniformed Services University of the Health Sciences (USUHS) and Zoetis Inc, USA is approved for vaccination of horses and several other vaccines based on outer membrane proteins G and F are under preclinical trials. Humanized monoclonal antibodies (Mab 102.4) specific to the HeV sG protein produced by USUHS, USA has shown promising results in animal studies.

The concluded Ebola virus outbreaks during 2014-16 of West Africa were a devastating failure where 11,000 people died due to the slow response of health authorities. Relatively weak health and surveillance systems in under-resourced countries in which NiV is circulating fuelled by high population density increases the risk of a pandemic. International public organizations must take accord from past mistakes and act proactively to contain such devastating outbreaks. The limited NiV cases are providing a learning opportunity to plan long-term strategy and enact adequate pandemic preparedness missing during Ebola outbreak. In Bangladesh, frequent viral transmission from bats to humans could provide an opportunity for the evolution of highly transmissible strain that can infect humans. WHO R&D Blueprint in 2018 listed NiV infection along with Ebola, Zika, MERS, Lassa and Crimean-Congo haemorrhagic virus that needs urgent research and development actions of priority epidemic threats. A draft has been issued by

WHO with a Nipah task force comprised of national and international experts that prioritizes the development of required countermeasures like diagnostics, therapeutics, and vaccines. Such concerted collaborative efforts are crucial to control NiV like infections where private sector investment is limited due to commercial aspects. The Coalition for Epidemic Preparedness Innovations announced on May 21, 2018 a US\$ 25 million investment funded by the governments of Germany,

Japan, and Norway and not for profit foundations like Bill & Melinda Gates Foundation and Welcome Trust, to accelerate work on NiV vaccine at USUHS, USA. World Organization for Animal Health also signed an agreement on May 30, 2018 with the Food and Agriculture Organization of UN and WHO to cooperate against human-animal-environment risks in view of the devastating zoonotic potential of NiV.