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REVIEW ARTICLE

Nipah Virus (NiV) Infection: Is Nepal Prepared for the Possible Outbreak?

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Abstract

After 20 years of the first Nipah Virus (NiV) outbreak in the world, it re-emerged as the outbreak in India. WHO has recognized NiV as a potent epidemic threat to human health. Both animal-to-human and human-to-human transmission of zoonotic NiV has been documented. Fruit bat of Pteropodidae family is the natural reservoir of the virus. Thus, the territorial habitat of these bats is the high risk zone of NiV outbreak. The symptoms are very nonspecific and the pathogenicity of NiV is yet to be fully understood. Diagnosis of NiV infection still relies on molecular techniques. Till date, no drugs or vaccines against NiV has been approved. Some research have presented arrays of the possible treatment and prevention option, but without sure shot implications. So, appropriate precautions are the only currently available prevention option. Nepal is yet to experience a NiV outbreak but that does not undermine the risk posed to the general population. High risk countries including Nepal should be well prepared to tackle the possible outbreak in future.

Keywords: Nipah virus, NiV, outbreak, Nepal

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Introduction

Outbreaks in glance

In the past few years, the outbreak of Ebola virus was on high rise throughout the world. In counter response against the virus, vaccine was developed and was being tested in high risk zones of Democratic Republic of the Congo on 19 May, 2018 [1]. Coincidentally on the same day, this was overshadowed by the news of the outbreak of the Nipah virus (NiV) in India. Initially three deaths were reported due to NiV infection. Since then 15 people have been tested positive for NiV, of which 13 are already dead. Other 16 suspected cases identified through contact tracing are under observation and at least 753 additional people are quarantined [2].

NiV is featured in the WHO list of blueprint priority diseases 2018 with potent epidemic threat demanding urgent research and development (R&D) action [3]. The first recorded outbreak of NiV occurred in 1998 in Malaysia following in Singapore in 1999. The outbreak involved severe respiratory illness in pigs and encephalitis in humans. Later outbreak involving human infections was reported from Bangladesh and India in 2001 [4,5]. Till date, more than 600 cases of NiV human infections has been documented. The outbreaks in Indian subcontinent have been recurrent [6]. Higher mortality of around 70% has been observed in Bangladesh and India, compared to mortality in Malaysia and Singapore outbreak [5]. This is probably due to higher engagement of the respiratory tract in the Bangladesh and India outbreaks, differences in pathogenicity of the viral strains and lack of advanced healthcare facilities [5].

Nipah Virus (NiV)

NiV is a member of the family Paramyxoviridae, genus *Henipavirus* [4,7]. The name Nipah virus originated from Sungai Nipah, a Malaysian village reporting the onset of an outbreak in 1998 [7]. NiV is a zoonotic virus. Both animal-to-human transmission (from infected bats/pigs) and human-to-human transmission have been documented. During Malaysian and Singaporean outbreaks transmission occurred from infected pigs, an intermediate host. However during Bangladeshi and Indian outbreak, transmission occurred through consumption of fruits/sap contaminated with infectious bat secretions and also through

human-to-human transmission. During this outbreak, no any intermediate host was reported owing to the lack of pig farms in the region [4,7].

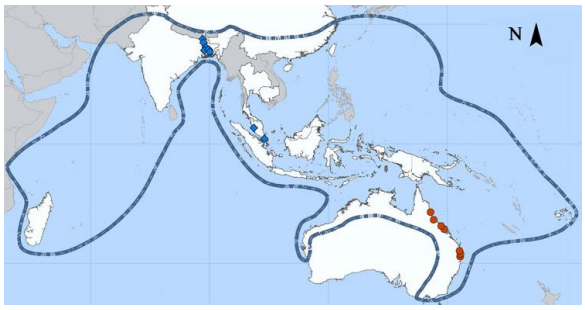

Figure 1. Adapted from "Nipah Virus Distribution Map," by Centers for Disease Control and Prevention (CDC) 2018, available at: https://www.cdc.gov/vhf/nipah/outbreaks/distribution-map.html. Copyright 2018 by the CDC. Adapted with permission.

Natural host

The natural hosts of NiV are fruit bats belonging to the Pteropodidae family, *Pteropus* spp. in particular [4,8]. Geographical distribution of NiV and *Pteropus* overlaps, ranging from Madagascar to Australia; covering South Asia, South-East Asia and Oceania region (Figure 1). Besides, African fruit bats of Pteropodidae family were also tested positive for NiV antibodies indicating further geographical distribution of NiV to African territory. NiV has also been tested positive in other animals including pigs, horses, goats, sheep, cats and dogs but only during the outbreaks [4]. Distribution map of these bats published by WHO includes Nepal however exact distribution and population of these bats are still to be studied and reported from Nepal.

Pathogenesis

NiV contains a negative-strand RNA. The non-segmented RNA contain six genes which encodes structural proteins of virus namely, fusion protein (F), glycoprotein (G), polymerase (L), matrix protein (M), nucleocapsid (N) and phosphoprotein (P). The P gene encodes additional three accessory proteins namely, C, V and W proteins [9,10].

V protein was the key determinants for pathogenesis in hamster and ferret infection model [11-13]. V proteins target multiple host proteins and thus suppress the host antiviral response. In addition, V proteins interact and suppress different signaling pathways. V protein suppress the dephosphorylation of melanoma differentiation-associated protein 5 (MDA5) thus inhibiting the activation of the interferon (IFN) β promoter [14-16]. V proteins also suppress the retinoic acid-inducible gene-I (RIG-I) dependent induction of IFN [17]. V proteins also block signaling through Toll-like receptors 7/9 (TLRs 7/9) and suppress IFN induction [18,19]. V proteins interact with IFN-responsive signaling pathway preventing activation and nuclear accumulation [20,21]. Similarly, C proteins regulate early host proinflammatory response thereby contributing virulence [22]. C protein was responsible for respiratory diseases in a ferret infection model [11,12]. The exact molecular mechanism of the pathogenicity of NiV is still to be revealed.

Signs and symptoms

The incubation time of NiV ranges between 4-14 days, and upto 45 days in some cases. Infections in human ranges from asymptomatic infection to acute respiratory infection, and fatal encephalitis in severe cases. Initial symptoms include headaches, influenza-like fever, myalgia (muscle pain), sore throat and vomiting. These symptoms are followed by acute encephalitis. Finally in severe cases, encephalitis and seizures occurs, leading to coma within 24-48 hrs. Fatality varies from 40% to 75%. Surviving cases are reported to demonstrate long-term sequel including persistent convulsions, personality change, seizure disorder, relapse and delayed onset encephalitis [4,7].

Diagnosis

Initial signs and symptoms of NiV infection are nonspecific, thus accurate diagnosis is challenging especially during an outbreaks. IgM Elisa for NiV, Real-time polymerase chain reaction (RT-PCR) and viral isolation are the tests employed for diagnosis [4]. These tests demands higher technical expertise and resources challenging the effectiveness of immediate counter measures during an outbreak.

Treatment

Currently, no drugs or vaccines are approved for NiV infection. Supportive care with intensive care is the only recommended treatment [4,7].

Favipiravir (T-705) has been demonstrated to inhibit NiV replication and transcription in Syrian hamster model, with twice daily oral administration for 14 days [23]. Ribavirin, which has broad spectrum anti-DNA and anti-RNA virus activity and can transverse the blood-brain barrier, was also reported to reduce mortality in an open-label trial [24].

Prevention

Vaccines have not been developed against NiV. However, routine and thorough disinfection of pig farms can prevent the infection. Also, avoiding the consumption of the bat eaten fruits or saliva/urine contaminated fruits/sap can prevent the infection. Thus, public awareness of the associated risk factors is the only measure to reduce risk of NiV infection. During outbreaks, suspected animal premises should be quarantined and infected animals should be culled. Also, healthcare workers caring suspected or confirmed NiV infected patients should adhere to standard infection control precautions [4]. Personal protection, such as masks, goggles, gloves, gowns, and boots, is advocated for field and farm workers of NiV risk zones. Personal protection should be accompanied by hand-washing and disinfection of equipments for better prevention [5].

Future prospects

Respiratory route administration of lipopeptides prevented NiV infection in both hamsters and non-human primates. Also, retention of peptides in respiratory tract avoided systemic delivery of NiV thus increasing safety and enhancing interventions [25]. Vaccines using a vesicular stomatitis virus vector have demonstrated protection against NiV in hamsters, ferrets and African green monkeys [26]. Recently in Australia, subunit vaccines using Hendra G protein have demonstrated protection against NiV in horses by producing cross-protective antibodies. This vaccine has potential for NiV protection in humans as well [7]. We could be on verge of testing vaccine against NiV soon.

Nepalese prospects

Till date no outbreak of NiV or NiV confirmed mortality has been documented within the territory of Nepal. No research has been done on surveilling antibodies against NiV in Nepalese human and/or bat population. However, Nepal harbors well distribution of *Pteropus* bat. Pig farms are widespread throughout the country. Nepal also has significant pork eating ethnic communities. This clearly outlines the possibility of surveilling NiV in bats and/or pigs of Nepal. Furthermore, Nepal and India share open border without medical surveillance and population mobility is higher in the border region. This further adds possible risk of viral transmission in Nepal. Thus, Nepal is at high risk of potential NiV outbreak.

Conclusion

Twenty years ago, NiV unveiled itself to the world causing significant morbidity and mortality. Initially NiV shattered the pig-farming industry in Malaysia, and is continually causing outbreaks in Indian subcontinent. The natural reservoir *Pteropus* bat is widespread, thus outbreaks can occur in any risk zones. The recent outbreak in India has again increased the concern of NiV as potential threat to human health. Governments and universities should fund research to develop vaccine or drug against NiV to neutralize the potential threat. All high risk countries including Nepal, should be well prepared to tackle the possible future catastrophe.

Conflict of Interest

The authors declare no any conflict of interest.

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Authors Contribution

Both authors DS and BB contributed to the work.

References

1 World Health Organization (WHO): **Ebola virus disease-Democratic Republic of the Congo: Update on Ring vaccination.** 2018, available at: http://www.who.int/csr/don/21-may-2018-ebola-drc/en/ [accessed 23/05/2018].

2 World Health Organization (WHO): **Nipah virus - India.** 2018, available at: http://www.who.int/csr/don/31-may-2018-nipah-virus-india/en/ [accessed15/06/2018].

3 World Health Organization (WHO): **R&D Blueprint. List of Blueprint priority diseases.** 2018, available at:

http://www.who.int/blueprint/priority-diseases/en/ [accessed 23/05/2018].

4 World Health Organization (WHO): **Nipah virus**. 2018, available at: http://www.who.int/news-room/fact-sheets/detail/nipah-virus [accessed 23/05/2018].

5 Ang BSP, Lim TCC, Wang L: **Nipah Virus Infection.** *J Clin Microbiol* 2018, 56(6):e01875-17. DOI: 10.1128/JCM.01875-17.

6 World Health Organization (WHO): **R&D Blueprint. Nipah R&D**. 2018, available at: http://www.who.int/blueprint/priority-diseases/key-action/nipah/en/ [accessed 23/05/2018].

7 Centers for Disease Control and Prevention (CDC): **Nipah Virus (NiV)**. 2018, available at: https://www.cdc.gov/vhf/nipah/index.html [accessed 23/05/2018].

8 Yob JM, Field H, Rashdi AM, Morrissy C, van der Heide B, Rota P, bin Adzhar A, White J, Daniels P, Jamaluddin A, Ksiazek T: **Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia.** *Emerg Infect Dis* 2001, **7(3):**439-441. DOI: 10.3201/eid0703.017312. PMID: 11384522.

9 Eaton BT, Broder CC, Middleton D, Wang LF: **Hendra and Nipah viruses: different and dangerous.** *Nat Rev Microbiol* 2006, **4:**23–35. DOI: 10.1038/nrmicro1323. PMID: 16357858.

10 Harcourt BH, Tamin A, Ksiazek TG, Rollin PE, Anderson LJ, Bellini WJ, Rota PA: **Molecular characterization of Nipah virus, a newly emergent paramyxovirus.** *Virology* 2000, **271(2)**:334–349. DOI: 10.1006/viro.2000.0340. PMID: 10860887.

11 Satterfield BA, Cross RW, Fenton KA, Agans KN, Basler CF, Geisbert TW, Mire CE: **The immunomodulating V and W proteins of Nipah virus determine disease course.** *Nat Commun* 2015, **6:**7483. DOI: 10.1038/ncomms8483. PMID: 26105519.

12 Satterfield BA, Cross RW, Fenton KA, Borisevich V, Agans KN, Deer DJ, Graber J, Basler CF, Geisbert TW, Mire CE: **Nipah Virus C and W Proteins Contribute to Respiratory Disease in Ferrets.** *J Virol* 2016, **90(14):**6326–6343. DOI: 10.1128/JVI.00215-16. PMID: 27147733.

13 Uchida S, Horie R, Sato H, Kai C, Yoneda M: **Possible role of the Nipah virus V protein in the regulation of the interferon beta induction by interacting with UBX domain-containing protein.** *Sci Rep* 2018, **8(1):**7682. DOI: 10.1038/s41598-018-25815-9. PMID: 29769705.

14 Davis ME, Wang MK, Rennick LJ, Full F, Gableske S, Mesman AW, Gringhuis SI, Geijtenbeek TB, Duprex WP, Gack MU: **Antagonism of the phosphatase PP1 by the measles virus V protein is required for innate immune escape of MDA5.** *Cell Host Microbe* 2014, **16(1)**:19–30. DOI: 10.1016/j.chom.2014.06.007. PMID: 25011105.

15 Andrejeva J, Childs KS, Young DF, Carlos TS, Stock N, Goodbourn S, Randall RE: **The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter.** *Proc Natl Acad Sci USA* 2004, **101(49)**:17264–17269. DOI: 10.1073/pnas.0407639101. PMID: 15563593.

16 Childs K, Stock N, Ross C, Andrejeva J, Hilton L, Skinner M, Randall R, Goodbourn S: **mda-5, but not RIG-I, is a common target for paramyxovirus V proteins.** *Virology* 2007, **359(1)**:190–200. DOI: 10.1016/j.virol.2006.09.023. PMID: 17049367.

17 Childs K, Randall R, Goodbourn S: **Paramyxovirus V proteins interact with the RNA Helicase LGP2 to inhibit RIG-I-dependent interferon induction.** *J Virol* 2012, **86(7)**:3411–3421. DOI: 10.1128/JVI.06405-11. PMID: 22301134.

18 Kitagawa Y, Yamaguchi M, Zhou M, Komatsu T, Nishio M, Sugiyama T, Takeuchi K, Itoh M, Gotoh B: **A tryptophan-rich motif in the human parainfluenza virus type 2 V protein is critical for the blockade of toll-like receptor 7 (TLR7)- and TLR9-dependent signaling.** *J Virol* 2011, **85(9)**:4606–4611. DOI: 10.1128/JVI.02012-10. PMID: 21345944.

19 Shaw ML, Cardenas WB, Zamarin D, Palese P, Basler CF: **Nuclear localization of the Nipah virus W protein allows for inhibition of both virus- and toll-like receptor 3-triggered signaling pathways.** *J Virol* 2005, **79(10)**:6078–6088. DOI: 10.1128/JVI.79.10.6078-6088.2005. PMID: 15857993.

20 Rodriguez JJ, Parisien JP, Horvath CM: **Nipah virus V protein evades alpha and gamma interferons by preventing STAT1 and STAT2 activation and nuclear accumulation.** *J Virol* 2002, **76(22)**:11476–11483. DOI: 10.1128/JVI.76.22.11476-11483.2002. PMID: 12388709.

21 Rodriguez JJ, Wang LF, Horvath CM: **Hendra virus V protein inhibits interferon signaling by preventing STAT1 and STAT2 nuclear accumulation.** *J Virol* 2003, **77(21)**:11842–11845. DOI: 10.1128/JVI.77.21.11842-11845.2003. PMID: 14557668.

22 Mathieu C, Guillaume V, Volchkova VA, Pohl C, Jacquot F, Looi RY, Wong KT, Legras-Lachuer C, Volchkov VE, Lachuer J, Horvat B: **Nonstructural Nipah virus C protein regulates both the early host proinflammatory response and viral virulence.** *J Virol* 2012, **86(19):**10766–10775. DOI: 10.1128/JVI.01203-12. PMID: 22837207.

23 Dawes BE, Kalveram B, Ikegami T, Juelich T, Smith JK, Zhang L, Park A, Lee B, Komeno T, Furuta Y, Freiberg AN: **Favipiravir (T-705) protects against Nipah virus infection in the hamster model.** *Sci Rep* 2018, **8(1):**7604. DOI: 10.1038/s41598-018-25780-3. PMID: 29765101.

24 Chong HT, Kamarulzaman A, Tan CT, Goh KJ, Thayaparan T, Kunjapan SR, Chew NK, Chua KB, Lam SK: **Treatment of acute Nipah encephalitis with ribavirin.** *Ann Neurol* 2001, **49**:810-813. DOI: 10.1002/ana.1062PMID: 11409437.

25 Mathieu C, Porotto M, Figueira T, Horvat B, Moscona A: **Fusion Inhibitory Lipopeptides Engineered for Prophylaxis of Nipah Virus in Primates**. *J Infect Dis* 2018, **218(2)**:218-227. DOI: 10.1093/infdis/jiy152. PMID: 29566184.

26 Satterfield BA, Dawes BE, Milligan GN: **Status of vaccine research and development of vaccines for Nipah virus.** *Vaccine* 2016, **34(26):**2971-2975. DOI: 10.1016/j.vaccine.2015.12.075 PMID: 26973068.