

## Mini Review

## Nipah Virus- A Rapidly Emerging Zoonoses: A Mini Review

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**Abstract:** Nipah virus is one of the deadliest viruses of Paramyxoviridae family, of the order Mononegavirales. The virus is harbored by *Pteropus* fruit bats and transmitted to pigs via partially eaten fruits or direct exposure to infectious bat secretions. Viral determinants that contribute to Nipah virus infection include V and W proteins where W protein plays a more prominent role. It is known for causing severe and rapidly progressive encephalitis and thus classified among BSL-4 organisms due to its high mortality rate and lack of vaccines and drugs. Due to wide spread primary host the potential for outbreaks to occur in new regions remains significant and suggests a serious potential for larger epidemics in the future. Therefore proper management and preventive measures are needed to be implemented by health care workers, as well as at the government level.

**Keywords:** Viral infection, Zoonoses, Fruit bats, Transmission, Nipah virus, BSL-4 organism, Paramyxovirus.

### INTRODUCTION

Among the deadliest viruses of the order Mononegavirales, nipah virus belongs to the Paramyxoviridae family of the genus Henipavirus [1]. It is highly pathogenic causative agent of respiratory and encephalitic disease in Southeast Asia [2]. Structure of virus consist of an envelope made of filamentous nucleocapsid made of major structural proteins i.e. fusion protein, glycoprotein, phosphoprotein, matrix protein and large protein (RNA polymerase). However, the genome of the virus is single stranded negative sense RNA which is a hallmark of the Paramyxoviridae family [3, 4]. *Pteropus* fruit bat serves as a reservoir for the virus. Zoonotic transmission occurs directly or through an intermediate host, however the outbreak was the result of pig-to-human transmission and requires between 4 and 30 days of incubation period [2-5]. Cases with the disease presents abrupt onset of fever, headache, dizziness, vomiting, respiratory and neurological illness including altered consciousness, encephalitis, hypotonia, areflexia etc. [5, 6]. The virus is well known for its outbreak in late 1998 and early 1999 in Malaysia and Singapore which resulted in 276 human cases with 106 deaths [2, 3, 5, 7]. The autopsy of fatal cases showed that CNS seemed to be a major target for the pathogen where it was found to be forming syncytium [3, 8, 9].

### PATHOGENICITY

Alpha/beta interferon constitutes STAT proteins (STAT1/STAT2 along with IFN regulatory factor-IRF9). It is part of innate immune system that provides cell protection against viral infections. ISGF3 transcription complex mediates the biological effect of Alpha/beta interferon [10, 11]. Thus IFN-induced, ISGF3-mediated transcription provides protection against broad range of viral infection, however most viruses have evolved to evade the INF induced protec-

tion [12, 13]. Viruses belonging to the Paramyxoviridae family causes infection by evading ISGF3 signals that are responsible for targeting STAT proteins in order to activate the Alpha/beta interferon [14]. Hence paramyxovirus-encoded V protein interacts with STAT proteins thereby blocking the interferons. V proteins were also observed to be responsible for various virulence activities such as blocking apoptosis, cell cycle arrest, IRF3 suppression and other protein-protein interactions [15-20]. Therefore V protein is a virulence and pathogenicity determining factor of paramyxovirus family [14]. V and W proteins both are responsible for bypassing the immune system but W protein is considered more potent as compare to V proteins. V proteins of nipah virus (Niv) inhibit the antiviral activity of RIG-I and MDA5 by phosphatase PPI and STAT through direct sequestration hence responsible for blocking only Inhibitor of kB kinase e (IKKe) signaling pathway [21-26]. Whereas Niv W proteins causes infection by impairing the function of IFN transcription factor 3, hence blocking Toll-like receptor 3 and Inhibitor of kB kinase e (IKKe) signaling pathways. It was also observed to be responsible in the suppression of IFN- $\beta$  and IFN-stimulated gene 54 (ISG54) promoters in HEK 293T cells [25, 26].

Furthermore, UBXLN1 A host protein, interacts with NiV V and thus increases the level of UBXLN1 protein by suppressing its proteolysis and suppresses the interferon activation [27]. Therefore Viruses that are missing V proteins are more prone to immune response both *in vitro* and *in vivo* and are non-lethal. Delay or alteration in the disease course was observed with viruses lacking W proteins. Such viruses also show reduced respiratory and elevated neurological disease [28].

### EFFORTS IN VACCINE AND DRUG DEVELOPMENT

Nipah virus is classified among BSL- 4 pathogens due to high mortalities in humans and its human to human transmission as well as absence of vaccine or specific antiviral treatment.

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Considering the pathogenesis and high mortality rate there are no vaccine available for human use. Recently a subunit HeV vaccine has been approved for animal use in Australia [29-31]. Also a viral envelop protein targeting monoclonal antibodies has been studied for animal and human use as post-exposure prophylaxis but the efficacy of treatment to human disease is yet to be studied [30-32]. Ribavirin is a broad spectrum antiviral drug used primarily for the treatment of hepatitis C and viral hemorrhage. The drug was reported to show effectiveness in Malaysian outbreak with 36% reduction in mortality [33] but also reported by others for its ineffectiveness against henipa virus infection [34-37]. Lately an analogue targeting RNA polymerase dependent on viral RNA has been developed named favipiravir. At present it is in use for influenza [38, 39] and has shown efficacy against Niv infected hamster models [40]. Furthermore the analogue has completed phase 2 trials as showed promising results against Ebola Virus infection in reducing the mortality rate [41].

Most of the vaccines for viral infection are in early stages of development. Using viral components and their expression in various viral vector for vaccine preparation is an attractive approach [42, 43]. Although currently there are no licensed vaccines available for the Niv infection but there are evidences that suggests that effective vaccine is attainable. Vaccines usually targets viruses having an incubation period of at least 5-7 days whereas shorter incubation period leads to unsuccessful vaccine development, therefore, incubation period of Niv is greater than 5-7 day threshold hence a potential vaccine is feasible [2]. Glycoprotein and Fusion outer membrane proteins are used for the development of vaccines to induce immune response in following animal models; African green monkeys (AGMs) hamsters, pigs, cats and ferrets etc. [44-50]. Vaccines using G proteins and Alhydrogel<sup>®</sup> and CpG oligodeoxynucleotide as an adjuvant exhibit potency against viral infected animal models. Equivac HeV<sup>®</sup> is an advanced vaccine of this category [51]. However, due to life threatening nature of virus, preparation of live attenuated vaccine with no possibility of reversion is a difficult task [28, 52].

#### LABORATORY DIAGNOSIS AND PREVENTION

For laboratory diagnosis of viral infection following methods are mainly used; serology, histopathology, immunohistochemistry, electron microscopy, polymerase chain reaction (PCR), and virus isolation. ELISA, imunohistochemistry and serology are safer methods as they don't intensify the viral infection and can be used as methods for initial screening purpose [53]. Due to limited treatment options for Nipha virus, focus on preventions of viral infections is significant. Following preventive strategies should be of main focus; farm animals should be kept far away from bat reservoirs, partially eaten bat fruits, overcrowding of farm with animals should be avoided, farms should be designed in areas that do not attract bats [54]. Execution of standard precaution and donning of proper personal protective equipment (PPE) by healthcare

workers while handling, caring and visiting suspected or confirmed NiV infection patient is important [55-57].

#### CONCLUSION

Nipah virus is rapidly emerging zoonotic virus that is classified among BSL-4 organisms due to its high mortality and absence of treatment. In recent year's outbreak of viral infection continue to occur in India and other Asian countries and due to widespread primary host, the potential for outbreaks to occur in new regions remains significant and suggests a serious potential for larger epidemics in the future. Prevention of viral infection is difficult in developing countries as it's a rare infection compared to other medical health threats faced by the people in low income areas. Improved understanding of the mechanism of zoonotic transmission from bats to humans might facilitate establish possible approaches to stop future introductions of the virus into the human population. The treatment currently used is just supportive and to develop a stable, vigorous and affordable drug or vaccine for the infection is one of the major challenges in order to limit the future epidemics, additionally restriction of activities that increases the interaction between animals, people and fruit bats could help prevent spread of infection.

#### CONFLICT OF INTEREST

Declared none.

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