Scientific Research Publishing

Advances in Infectious Diseases, 2023, 13, 283-290
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Nipah Virus: A Zoonotic Virus Transmitted from Bats and Pigs, Causing an Epidemic in Southeast Asia

Hongting Lin

Poly Prep Country Day School, Brooklyn, New York, USA
Email: linh24@polyprep.org

How to cite this paper: Lin, H.T. (2023) Nipah Virus: A Zoonotic Virus Transmitted from Bats and Pigs, Causing an Epidemic in Southeast Asia. *Advances in Infectious Diseases*, **13**, 283-290.
https://doi.org/10.4236/aid.2023.132026

Received: April 14, 2023
Accepted: June 11, 2023
Published: June 14, 2023

Abstract

Nipah Virus (NiV), a member of the Paramyxoviridae family, is one of the most infectious zoonotic viruses in Southeast Asia. First recorded in Malaysia in 1998, the NiV outbreak infected hundreds of people, with an almost 50% death rate. The virus is transmitted through direct contact with contaminated subjects and infecting the human respiratory system. Ephrin B2 and B3, the surface glycoproteins on the host cell, have been the primary and the most effective route for viral entrance. Binding with viral surface G protein, the F protein triggers, enabling viral-host fusion. Until now, NiV vaccines are not yet available in the public market, however, preventions such as avoiding direct contact and masking are advised.

Keywords

Nipah Virus, Zoonotic Transmission, Ephrin-B2, Ephrin-B3, Viral Outbreaks, Clinical Outcomes, Animal Reservoir

1. Introduction

Viruses infect cells by inserting their genetic material (RNA or DNA) into the host cell to take over cellular function. After inserting the viral genome into the host genetic material, the viral replication cycle, which requires transcription and translation of the viral genome, is completed to produce more copies of viral DNA/RNA. Following replication, the assembly of virions occurs. Virions are viruses that are fully capable of infection. This happens when genomes are assembled into protein shells called capsids, and at the same time as maturation, in which virions become infectious. The virus is ready to be released once matured; the enveloped virions are released by budding the host cell membrane.

A particular viral family, the Paramyxoviridae family, infects cells by binding viral surface proteins (glycoprotein G and fusion protein F) with the target surface receptors, proteins embedded in the cell membrane that enable cell signaling by binding with extracellular molecules. A specific viral member of this family, the Nipah Virus (NiV), is a highly infectious pathogen that transmits from animals to humans and causes fatal diseases like encephalitis or severe respiratory illness. NiV is a new virus first identified in 1998, but has a similar structure as the Hendra virus (HeV): similar wide host range, cross-reactive antibodies. (Figure 1) But neither shows hemagglutinin, a surface glycoprotein that promotes viral-host fusion, nor presents neuraminidase, a surface enzyme that cleaves acids on the target cells, essentially paving a pathway for a convenient viral entrance. [1]

The first NiV human outbreak was recorded in a pig farm in Perak, Malaysia, in 1998, followed by multiple outbreaks in neighboring states including Negri Sembilan and Bukit Pelandok. [1] During the Malaysian outbreaks, a total of 265 infected patients were identified, including 105 deaths. The majority of the infected patients were adult males with direct interactions with pig farms, suggesting pig transmission to humans. Thus, NiV-infected pigs were immediately isolated from the farm, and the infection rate among pigs correspondingly declined. Although the epidemic was small-scale, the high mortality rate caused panic and increased attention to this emerging virus. [2]

2. Baltimore Type and Its Correlation to NiV

Baltimore Type is a system that classifies viruses based on how they use virus messenger RNA (mRNA). Seven Baltimore groups are used to determine the virus characteristics: whether a virus contains DNA or RNA, whether the genome is double or single-stranded, and whether they're positive or negative. This type of classification is practical to group viruses that are similar in replication and transcription. It is also useful to understand how a virus, in this case, NiV, infects cells. The reason for the differing severity NiV of infections in humans and pigs could be the varying host cells that support viral replications. In pig infections, NiV infecting the host cells results in the accumulation of intracellular viral RNA, but not enough extracellular viral release. However, in humans, NiV infection first happens in human lungs, then replicates itself in other organs.

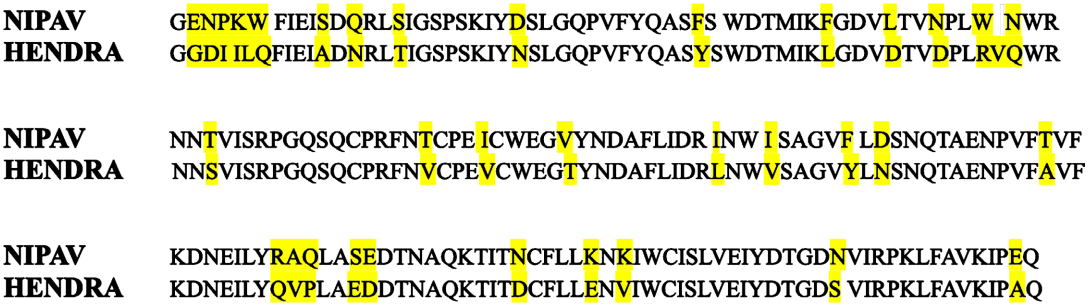

Figure 1. Protein sequencing of NiV and HeV shows 36 differences (highlighted) and 145 similarities. [3]

Previous studies show viral replication in lung fibroblast cells, suggesting that NiV could infect other surrounding cells immediately after entering the host through cell-to-cell spread. [4] For both animal reservoirs, NiV infects endothelial and neuron cells, though transmitting through neuron cells is far less efficient because they have a lower ability to support the infection. [5]

3. NiV Viral Entry into Target Cells with Surface Glycoproteins Ephrin-B2 and Ephrin-B3

Ephrin B2 and Ephrin B3 (B-class ephrins), the functional binding receptors in the host cells that facilitate NiV viral entry, are highly expressed in neural cells because it controls nervous system development and manages brain maintenance. Once NiV binds to Ephrin receptors, it's easier for the virus to enter the membrane and control the cellular machinery. (**Figure 2**) Human Ephrin-B2 and B3 belong to a large portion of the receptor protein-tyrosine kinase subfamily. Ephrin-B2 expresses in different cell types, including endothelial cells, smooth muscles around arteries, placental tissues, and neurons. Ephrin-B3 is expressed in lymphoid cells which may explain the NiV-induced acute lymphoid necrosis. [6] The Eph receptors are crucial in signaling and bidirectional cellular transport because their rigidity provides a strong scaffold for viral attachments that offers an advantage for their use as viral attachments. [7] The surface glycoprotein G of the virus detects and binds to the Ephrin-B2 or Epherin-B3 protein receptors on the host membrane. (**Figure 3**) The F protein triggers, inserting its fusion peptide into the host-membrane, mediating viral-host fusion, and merging the viral envelope and cell membrane, thus completing the viral-host fusion

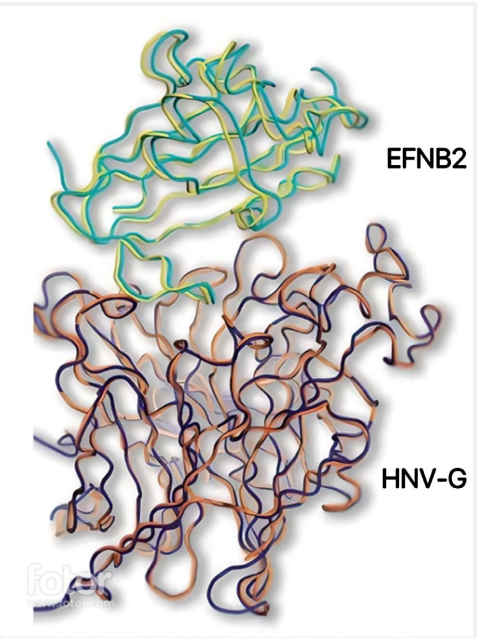

Figure 2. The top structure represents the interaction between NiV G protein (blue) and Ephrin B2 (yellow); the bottom structure represents HeV G protein (orange) and Ephrin B2 (cyan). [8]

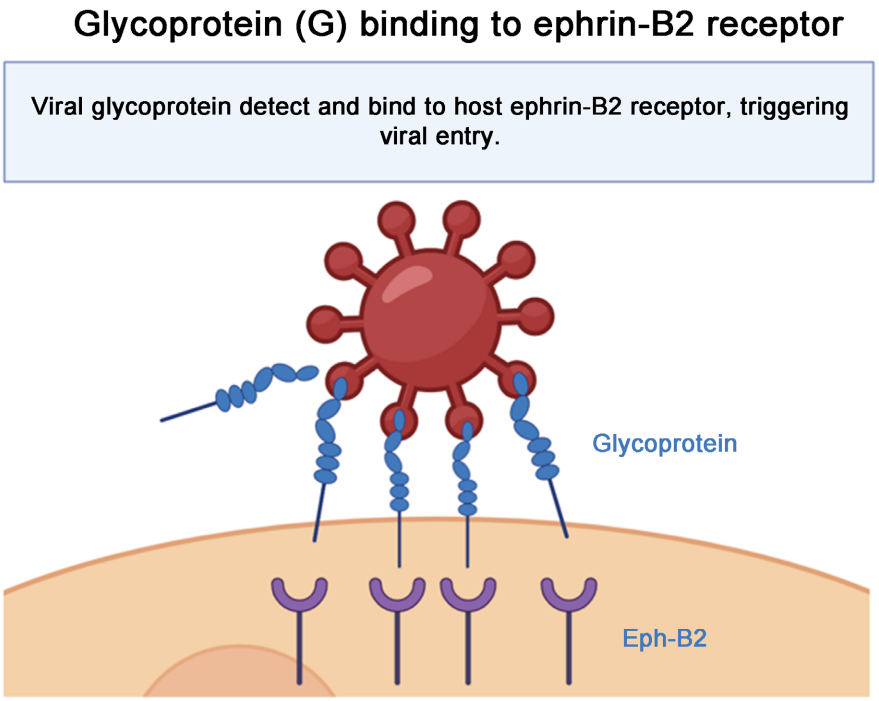

Figure 3. NiV viral infection in the host cell through the binding of G protein and Ephrin B2.

[7]. During the viral entry, the fusion (F) protein maintains the virion in a metastable state pre-fusion. One potential uncertainty regarding NiV entry is the knowledge gap between the specificity of how exactly viral G protein receptors manage to bind to F trigger protein and thus later enable membrane fusion.

4. The Mutation within the G-H Loop of Ephrin-B2 Has Been Discovered to Enhance the Viral Entry and Viral Fusion

Ephrin-B2 is shown to be more involved with attaching to the NiV glycoproteins because it displays as a more stabilized complex upon entrance compared to Ephrin-B3. [2] The G-H Loop is a hydrophobic surface on the host cell that plays a crucial role in virion attaching or detaching from the cell surface; it sits in the center of the G protein/ephrin and is structurally rigid in Ephrin B2. By being closely related to the viral infection cycle, G-H loop in turns support NiV entry and advance the Ephrin-B2 binding. The G-H loop undergoes conformational changes upon normal G-protein binding, and its rearrangement enables the proteins to fit into their corresponding pockets. Based on the result presented in previous studies, most of the ephrin-B2 mutations outside the G-H loop present little inhibition/effect on NiVpp (NiV pseudotyped particles) infection. However, the majority of the mutations within the G-H loop could support NiVpp entry, such as S121A, P122A, L124A, and W125A. Among all mutants, the L124A mutant shows the most significant enhancement of virus entry. [9]

5. Clinical Outcomes in Humans

Symptoms of NiV range from asymptomatic to severe. Majority of the patients

experience cough, cold, dyspnea, fever, vomiting, dizziness, abnormal brain stem, reduced reflex, and doll's eye reflex; some experience encephalitic syndrome with headache, pyrexia, and other neurological symptoms. [1] The incubation period (usual time period before any symptoms are perceived) is 4 - 14 days; however, a period of as long as 45 days has been reported. Most people fully recover from encephalitis, however, 20% of the survivors have reported continued issues in their neurological systems such as personality change.

Although the NiV epidemic swept through some Asian countries in the late 20th century and infected countless civilians, there are still no treatments to prevent such epidemics. No specific antivirals or vaccines exist yet, only intensive supportive care is recommended for people infected with NiV. Ribavirin and acyclovir (antiviral medications) were given to infected patients in some studies, and results showed that mortality rate was reduced by up to 36% when given Ribavirin, though acyclovir impact is still unclear.

Scientists have been trying to tackle NiV treatment through experiments with model organisms such as hamsters infected with NiV. At least eight vaccine candidates have been tested on animal models: vaccines encoding NiVm F and NiVm G protect hamsters and pigs from NiVm. [10] Virus vaccines expressing NiVM G completely protected hamsters against homologous NiVM challenge, and virus vaccines expressing NiVB G completely protected hamsters against exposure to NiVB and NiVM. There are still problems in extending these vaccines to human populations. First, the vaccines are too costly. To prevent NiV infection, multiple-doses of injection are needed, making them costly and logistically challenging for low-income families. Second, there would be a limited time to deploy multiple doses during a natural outbreak of NiV. Therefore, the most ideal vaccine would only require a single injection that results in a rapid protection. [10]

6. General Zoonotic Transmission

An animal reservoir is a habitat where an agent lives and grows before leaving through an exit portal and initiating its transmission. Animal reservoirs typically exist with extensive animal-to-animal transmissions, with humans sometimes being incidental hosts. Zoonotic transmission, a cross-species spillover, is the transfer of infectious diseases from vertebrate animals to humans in a natural environment. To determine whether a virus is more adapted to one species or another, the codon adaptation index (CAI) and relative codon deoptimization index (RCDI) are used to quantify the codons used by the virus. A high CAI means the virus is more adapted to the host than those with low CAI values. In contrast, a low RCDI value means a high adaptation, and a high RCDI value indicates a low adaptation to the host, often accompanying infections (**Table 1**). A comparative analysis shows that the African green monkey has the highest CAI value for NiV, with bats and humans the second highest. According to the data, the human host is the third best at replicating viruses and based on the CAI values,

Table 1. CAI values in each host species for NiV, HeV, CedV, and MojV. The higher the value, the more adaptive the virus in that species. African Green Monkey is shown to have the highest CAI value amongst four viruses, followed by bats and humans. [11]

Species	Average CAI			
	NiV	HeV	CedV	MojV
Homo Sapiens (Humans)	0.728	0.738	0.746	0.734
Pterous Vampyrus (Bat)	0.749	0.746	0.757	0.745
Equus Caballus (Horse)	0.653	0.649	0.666	0.649
Canis Familiaris (Dog)	0.66	0.497	0.501	0.487
Sus Scrofa (Pig)	0.613	0.612	0.627	0.611
Felis Catus (Cat)	0.657	0.656	0.668	0.661
Mesocrictus Auratus (Hamster)	0.674	0.663	0.685	0.668
Mustela Putorius (Ferret)	0.581	0.576	0.597	0.579
Simiri Sciureus (Squirrel Monkey)	0.597	0.591	0.61	0.593
Chelorocebus Aethiops (African Green Monkey)	0.755	0.75	0.764	0.748

highly adapts to the virus. [11]

7. NiV Zoonotic Transmission

NiV transmits through multiple routes: animal-to-animal, animal-to-person, and person-to-person. The transmissions within animals were mostly observed among the flying foxes to farm pigs; person-to-person transmissions have been recorded but not been widely observed in the past outbreaks. Therefore, more research attention is paid to the zoonotic transmission of animal-to-person. Multiple factors influence the transmission of the Nipah Virus from infected animals to humans. First, close contact with infected animals and animal reservoirs, such as farm pigs, is the main source of infection in humans. The majority of the transmissions were observed through respiratory tracts through this close contact, though some cases have been proven as oral routes. Second, the consumption of contaminated food–such as pork products made from infected pigs, and food containing bat secretions–is also one of the results of mass NiV infections. Finally, some studies indicate that close and prolonged contact with the tissues of infected animals could also result in NiV infection. [1]

The NiV antigen was first identified in Pteropus fruit bats, known as flying fox, acting as a natural host reservoir which is the organism the pathogens survive in. With bat's excretion, the pathogen was further transmitted to domestic farm pigs as an indirect infection. The farm pig thus takes the role of mediator to humans, completing the zoonotic transmission. Previous studies showed that a considerable number of infected humans were in contact with pig farming and had close contact with infected pigs. [1] Humans are susceptible to NiV, and the RNA virus has potential to mutate. Thus the characteristics of NiV has potential

to enhance the global pandemic due to its ability through zoonotic transmission. If a human-adapted strain were to infect communities in South Asia, the high human population would rapidly spread the infection across the globe. [10]

Even though we couldn't prevent NiV molecularly, there are still ways in which physical isolation could result in a reduced infection rate. The virus is mainly transmitted through the oronasopharyngeal route (through the mouth) and distributes itself in the human airway—the outbreak in India showed symptoms of respiratory disease, suggesting the damage in lung epithelial cells. [12] Thus we could halt the spread of NiV through the following: preventing human-to-human transmission by limiting contact with infected people; regular hand washing after visiting infected patients; preventing animal-to-human transmission by wearing sanitary equipment such as gloves, keeping distance from infected pigs and protecting pig farms and pig sheds from the fruit bats as much as possible; Preventing bat transmission by avoiding bats' access to fresh food products, and discarding fruits with bat bites and bat excretion. More importantly, masking can partially prevent NiV from entering the respiratory system.

8. Conclusion

Recently, zoonotic transmission has impacted everyone's life for the past three years as COVID-19 swept across the population. But other zoonotic transfer is occurring—as evidenced by Nipah Virus (NiV), which caused frightening and chaos around Southeast Asia resulting in the death of thousands of people. Here we show the NiV viral entrance into animal reservoirs and viral mutation as it transmits from animal hosts to humans. The experimental NiV vaccine is being tested in clinical trials to evaluate its ability to generate an immune system in adults. Although no official vaccines are not yet available to prevent the Nipah virus, we can still take precautions to potentially avoid outbreaks.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Sharma, V., Kaushik, S., Kumar, R., Yadav, J.P. and Kaushik, S. (2018) Emerging Trends of Nipah Virus: A Review. *Reviews in Medical Virology*, **29**, e2010. https://doi.org/10.1002/rmv.2010

[2] Looi, L.-M. and Chua, K.-B. (2007) Lessons from the Nipah Virus Outbreak in Malaysia. *The Malaysian Journal of Pathology*, **29**, 63-67.

[3] Priyadarsinee, L., Sarma, H. and Sastry, G.N. (2022) Glycoprotein Attachment with Host Cell Surface Receptor Ephrin B2 and B3 in Mediating Entry of Nipah and Hendra Virus: A Computational Investigation. *Journal of Chemical Sciences*, **134**, Article No. 114. https://doi.org/10.1007/s12039-022-02110-9

[4] Chang, L.-Y. and AbuBakar, S. (2009) Nipah Virus: Phylogeny and Replication.

Neurology Asia, **14**, 63-66.

[5] Wong, K.T., *et al.* (2002) Nipah Virus Infection: Pathology and Pathogenesis of an Emerging Paramyxoviral Zoonosis. *The American Journal of Pathology*, **161**, 2153-2167. https://doi.org/10.1016/S0002-9440(10)64493-8

[6] Xu, K., Broder, C.C. and Nikolov, D.B. (2012) Ephrin-B2 and Ephrin-B3 as Functional Henipavirus Receptors. *Seminars in Cell & Developmental Biology*, **23**, 116-123. https://doi.org/10.1016/j.semcdb.2011.12.005

[7] Flanagan, J.G. and Vanderhaeghen, P. (1998) The Ephrins and Eph Receptors in Neural Development. *Annual Review of Neuroscience*, **21**, 309-345. https://doi.org/10.1146/annurev.neuro.21.1.309

[8] Bowden, T.A., *et al.* (2008) Structural Basis of Nipah and Hendra Virus Attachment to Their Cell-Surface Receptor Ephrin-B2. *Nature Structural & Molecular Biology*, **15**, 567-572. https://doi.org/10.1038/nsmb.1435

[9] Yuan, J., *et al.* (2011) Mutations in the G-H Loop Region of Ephrin-B2 Can Enhance Nipah Virus Binding and Infection. *Journal of General Virology*, **92**, 2142-2152. https://doi.org/10.1099/vir.0.033787-0

[10] Foster, S.L., Woolsey, C., Borisevich, V., Agans, K.N., Prasad, A.N., Deer, D.J., Geisbert, J.B., Dobias, N.S., Fenton, K.A., Cross, R.W. and Geisbert, T.W. (2022) A Recombinant VSV-Vectored Vaccine Rapidly Protects Nonhuman Primates against Lethal Nipah Virus Disease. *Proceedings of the National Academy of Sciences of the United States of America*, **119**, e2200065119. https://doi.org/10.1073/pnas.2200065119

[11] Khandia, R., *et al.* (2019) Analysis of Nipah Virus Codon Usage and Adaptation to Hosts. *Frontiers in Microbiology*, **10**, Article 886. https://doi.org/10.3389/fmicb.2019.00886

[12] Lamp, B., *et al.* (2013) Nipah Virus Entry and Egress from Polarized Epithelial Cells. *Journal of Virology*, **87**, 3143-3154. https://doi.org/10.1128/JVI.02696-12