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NIPAH VIRUS INFECTION: A DEADLY ZOONOSIS

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1. INTRODUCTION

1.1 Overview

Nipah virus (NiV) is a highly pathogenic zoonotic paramyxovirus that emerged in 1998 as the causal agent of a respiratory disease and an acute febrile encephalitis in humans.[1, 2]

Among the NiVs known to cause disease in humans, there are two major genetic lineages, i.e., NiV Malaysia (NiV-MY) and NiV Bangladesh (NiV-BD).[4]

The first cases began in late September 1998 in villages near the city of Ipoh in the state of Perak, West Malaysia, where pig farming was a major industry.[4]

It was spread by the movement of sick pigs to a second epicenter, 160 miles south in the state of Negri Sembilan, Malaysia.[7]

The outbreak subsequently spread to involve abbatoir workers in Singapore.[8] where pigs originating from Negri Sembilan were held and slaughtered.[10]

The virus was subsequently named Nipah virus after Kampung Sungai Nipah (Nipah River Village), where the first viral isolates were obtained.[7,11] This strain of virus was of NiV Malaysia (NiV-MY).

Soon after discovery of the virus, pteropodid fruit bats were identified as the natural reservoir hosts of the virus[14], and there was greater understanding of how NiV had infected pigs. Fruits partially eaten by bats may have been dropped or thrown into pigsties and subsequently infected the pigs that consumed the contaminated fruit.[4]

NiV was recognized in Bangladesh first in 2001 and nearly annual outbreaks have occurred in that country with periodic disease events in eastern India bordering to Bangladesh.[16]

A putative NiV also caused an outbreak of the disease in horses and people in the Philippines in 2014.[4]

In India, there was a large outbreak (66 probable cases and 45 deaths) in Siliguri, West Bengal in 2001 and another smaller outbreak (five cases, 100% fatality) in 2007 in Nadia district, West Bengal. In May 2018, an outbreak of NiV was declared in Kozhikode and Malappuram districts of Kerala.[17]

A new case of a 23-year-old student was detected again on 4 June 2019 in Kochi.

A total of 276 cases were reported with 106 fatalities (38%) in Malaysia, but case fatalities in later outbreaks in India and Bangladesh were associated with significantly higher case fatality rates of 43–100%.[17]

The emergence of NiV into the pig population and subsequently into the human population is believed to be due to changes in ecological conditions. Urbanization, deforestation and drought resulting in a shortage of resources for bat populations could have compelled bats to move from their natural habitats to agricultural areas.[20]

The identification of Ephrin B2 as a henipavirus receptor not only provides an explanation for the diverse host range of these viruses, but also helps to explain the observed systemic distribution of viral antigen particularly in arterial endothelial cells and smooth muscle.

The direct contact with pigs or fresh pig products was responsible for NiV transmission to humans, confirming preliminary observations by health workers in Malaysia.[2]

Investigation of different Nipah outbreaks in Bangladesh have identified different routes of transmission including climbing trees (probably contaminated with infected date palm sap), contact with sick persons, and contact with sick animals.[24-28]

Clinical signs and symptoms starts from headache, fever, dizziness, and vomiting, which in later on develops into severe encephalitis.[3]

There are currently no drugs or vaccines specific for Nipah virus infection. Intensive supportive care is recommended to treat severe respiratory and neurologic complications.[3] Ribavirin, m102.4 monoclonal antibody, favipiravir and remdesivir are being studied as treatments as of 2019.[29]

1.2 OBJECTIVE

The objective of this review is.

- To describe outbreaks of Nipah virus with respect to place of origin, transmission, pathogenesis, clinical features and types of diagnostic test.
- To advocate this information to the community, health care providers and researchers in order to have a better understanding and preparedness for any future outbreaks.
- To mitigate risk of spillover.
- To educate and to encourage behaviors which lessen the odds of disease spillover.
- To study about Nipah virus in animals and people, and the types of human activities like agricultural expansion, that can allow it to jump from bats to people, before it becomes a global pandemic.

Understanding pandemics and preventing them requires an understanding of each step in this chain of events.

As the vaccines drug are under trials it is better to protect ourselves by controlling the future outbreaks.

1.3 Classification

Order: Mononegavirales. **Family**: Paramyxoviridae. **Subfamily**: Paramyxovirinae. **Genus**: henipavirus.

Species: Nipah Virus.

NiV is classified under the genus henipavirus, within the subfamily Paramyxovirinae of family Paramyxoviridae. Hendra virus belongs to the same genus henipavirus and shares a high degree of sequence homology with the nipah virus and have similar genomic organization.[31]

1.4 Natural Host

Fruits bats (macrochiroptera) belonging to the family pteropodidae, of the pteropus genus are the natural host of nipah virus. There is no apparent disesase in the fruit bats.

Pteropus bats are widely distributed in tropics and subtropics of Asia, Australia, Indonesia, Madagascar and a number of remote oceanic islands in both the Indian and Pacific Ocean.

Fig 1.4: Natural Host Pteropus Bats Table 1.4 Nipah virus and fruit bats.

Location	Bat species	Evidence of infection
East coast, Australia.	Pteropus conspicillatus, P. alecto, P. scapulatus, P. poliocephalus	Serology
Papua New Guinea.	Dobsonia moluccense, P. neohibernicus, D. andersoni, P. capistratus, P. hypomelanus, P. admiralitatum	Serology
West coast, Peninsular Malaysia	Cynopterus brachyotis, Eonycteris spelaea, P. hypomelanus, P. vampyrus, Scotophilus Kuhlii	Serology (ELISA) and serum neutralizing test
Tioman Island, East coast, Peninsular Malaysia.	Pteropus hypomelanus	Virus culture, gene sequencing
Bangladesh	P. giganteus	Serology
Thailand	Pteropus hypomelanus, P. lylei, P. vampyrus, Hipposideros larvatus	Serology (ELISA) and RT-PCR
Cambodia	Pteropus lylei	Serology (ELISA), seroneutralizing test and PCR
Sumatra, Java, Indonesia	Pteropus vampyrus	Serology (ELISA), virus neutralizing test
Madagascar	Eidolon dupreanum, Pteropus rufus	Serology (ELISA), serum neutralization test,
Yunan and Hainan Island, China	Myotis sp., Rousettus leschenaultia,	Serology (ELISA), serum neutralizing, PCR
India	Pteropus giganteus	Serology (ELISA) and serum neutralizing test
Ghana	Eidolon helvum, Epomophorus gambianus,	Serology (Luminex)
	Hypsingathus monstrosus	Multiplexed binding assay

1.5 Species susceptibility

Humans, pigs, bats, dogs, cats, goats and horses are known to be susceptible to NiV infection. NiV infection has been reported also in sheep, but not confirmed and remains controversial.[13,15]

Clinical disease is observed in experimental conditions in ferret (Mustela putorius furo), guinea pig (Cavia porcellus), squirrel monkey (Saimiri sciureus), African green monkey (chlorocebus aethiops), hamster (Cricetinae) and in suckling mouse (Mus musculus).

2.1 EPIDEMIOLOGY AND DISEASE OUTBREAKS

2.1.1 Malaysia

Human NiV infection was first identified in Malaysia from 1998 to 1999.[18]

The first outbreak began in late September 1998 in villages near the city of Ipoh in the state of Perak, West Malaysia, where pig farming was a major industry.[4]

Cases continued to occur in this region until early February 1999.[4]

Another similar second outbreak was observed in a town of Sikamat of state Negri Sembilan, Malaysia in December 1998 to January 1999.[1,7]

The third and largest cluster began near the city of Bukit Pelandok in the same state in December 1998.[21]

In March 1999, a new virus (NiV) was isolated from the cerebrospinal fluid (CSF) of a patient from Sungai Nipah village.[2] Subsequently, the virus was named as Nipah, after the village from where the virus was first isolated, Kampung Sungai Nipah.[2]

During these outbreaks in Malaysia, a total of 265 Nipah encephalitis patients were confirmed out of which 105 (39.6%) deaths were reported.[19]

Culling of over a million pigs followed by disposal by deep burial and decontamination with quick lime, along with other control strategies was successful in controlling the outbreak.[34]

Dogs were also found to be commonly infected[35] and dogs dying on farms was found to be another risk factor.[36]

2.1.2 Singapore

In the meantime, in late February1999, the outbreak had spread to Singapore due to import of infected pigs from infected area of Malaysia. In early March 1999, 11 pig farmers in Singapore were diagnosed NiV positive with one fatality. All those farmers were involved in the import of live pigs from NiV infected part of Malaysia and had close contact history with

the infected pigs.[1,37]

The nucleotide sequences of reverse transcription-PCR (RT-PCR) products isolated from the Singaporean cases were identical to Nipah virus sequences from Malaysian cases and pigs[38] established a causal association between human Nipah virus infection in Singapore and Malaysia.

The outbreak ended with the ban on importation of live pigs from Malaysia, and the ban on importation of live pigs, pork, and pork products from peninsular Malaysia is still in place to this day.[4]

NiV infection has not been reported directly in man or pig in Indonesia, but exposure of Pteropusvampyrus bats to NiV has been reported. Thus in Indonesia, there is every possibility of disease spread from the carrier bats to pig or man.

2.1.3 Bangladesh

The epidemiology of NiV is significantly different in Bangladesh. Since 2001, seasonal outbreaks of NiV have occurred in Bangladesh in the winter months, primarily in 20 districts[23] in central and north-western Bangladesh (the_Nipah belt‘), where the majority of spillover events occur.[30]

The first NiV outbreak was reported in April-Meherpur 2001 from a village in district Meherpur, Bangladesh with 13 confirmed cases and 9 (69.2%) deaths.[24]

Thereafter, districts affected by NiV infection between January 2003 to February 2013 were: Naogoan, Rajbari, Faridpur, Tangail, Thakurgaon, Kushtia, Pabna, Natore, Naogaon, Manikgonj, Rajbari, Faridpur, Gaibandha, Rangpur, Nilphamari, Madaripur, Gopalganj, Lalmohirhat, Dinajpur, Rangpur, Comilla, Joypurhat, Rajshahi, Gaibandha, Rajshahi, Pabna, Jhenaidah and Mymensingh. Few districts of Bangladesh observed repeated outbreaks.[20]

During this outbreak Pteropus bats was identified as the reservoir.Outbreaks coincide with sap harvesting season (December–May).[17]

Person- to- person spread is an important mode of transmission in Bangladesh and has been identified in all outbreaks. The largest person-to-person outbreak occurred in Faridpur in 2004.[33]

A total of 13 Nipah annual outbreaks have been observed from various parts of Bangladesh till 2015, resulting 261 laboratory confirmed cases with 199 (76.2%) deaths.[24,19,32]

2.1.4 India

Three outbreaks of NiV have been reported in India since 2001.

In early 2001, there was an outbreak of infectious febrile illnesses, occurred in and around of Siliguri city of northern part of West Bengal.[39] Total 66 cases and 45 deaths were reported in this outbreak.[16,43]

As per patient observation and history, all the cases were adults without any history of pig or other animal exposure and some evidence of nosocomial transmission. No role of pigs in NiV infection transmission was found, and the outbreak spread mainly from person-to-person contact specifically in hospital settings. The second outbreak of NiV was surfaced during April, 2007 at village Belechuapara, near to Bangladesh border area in Nadia district of the West Bengal.[41]

The 2007 outbreak consisted of one person who contracted the disease due to consumption of alcohol made from date palm and all the others, including one healthcare worker, acquired the disease from the first case.[41] This outbreak was limited to five persons only, but case fatality rate was 100% as all infected persons died within a week of infection.[19,20]

On 19 May 2018, a Nipah virus disease (NiV) outbreak was reported from Kozhikode district of Kerala, India. This is the first NiV outbreak in South India.[43]

The human-to-human transmission of infection occurred through droplet infection. The two costal districts (Kozhikode and Malappuram) of Kerala state were affected due to NiV. As per the reports of Directorate of Health Services, Kerala, there were 13 deaths out of 14 confirmed cases in Kozhikode district, and three deaths out of four confirmed cases were reported from Malappuram district.[44]

NiV was confirmed upon laboratory testing using RT-PCR. Genetic analysis at the early stage confirmed NiV etiology and that the epidemic strain showed close resemblance to the BD strain of NiV.[43] There have been 17 deaths and 18 confirmed cases as of 1 June 2018.[43] All these three NiV outbreaks resulted in 67 (75.2%) deaths.

Again by the end of May, 2019 a young student was admitted with Nipah symptoms in Ernakulam district of Kerala and was confirmed Nipah-infected on 4 June 2019. The student survived and on 23 July 2019 left the hospital free of the disease after nearly 2 months of treatment. The infection appears to have been contained due to the early identification and caution by health department of Kerala Government.[45]

2.1.5 Philippines

An outbreak of NiV virus occurred in the southern part of Philippines affecting two villages of Mindanao in 2014.

The case definition was met by 17 persons (11 with encephalitis, 5 with influenza-like illness, and 1 with meningitis). Testing for a range of neurotropic pathogens was negative for all agents except for henipaviruses. Neutralizing antibodies against NiV and IgM against NiV were also detected in 3 patients. It was thought that virus transmission to humans was from direct exposure to infected horses, contact with contaminated body fluids during slaughtering of sick horses, and/or consumption of undercooked meat from infected horses.[46]

The NiV outbreak in Philippines was responsible for total 17 laboratories conformed cases with nine (53%) deaths.[19,46]

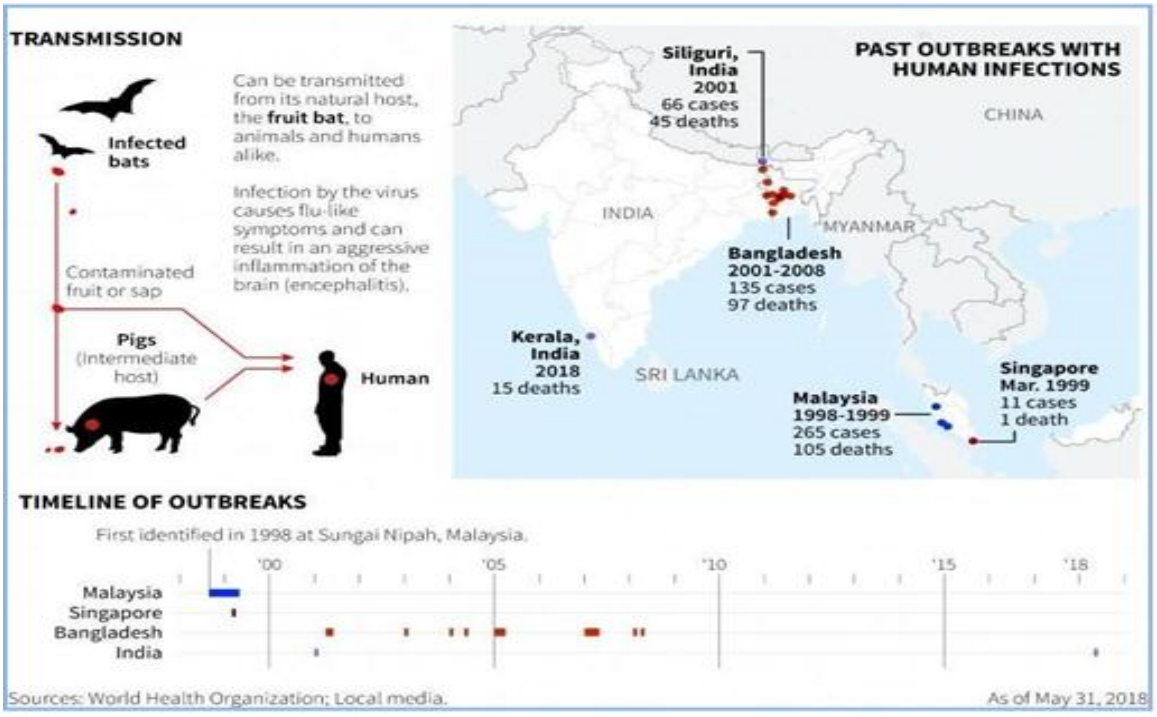

Fig 2.1. Timeline of Nipah Virus outbreaks.

Table 2.1 Epidemiological data of nipah virus.

S. No	Year/Month	Country	Location	No. of cases	No. of deaths	Case fatality rate, %
1	Sep 1998- April 1999	Malaysia	Perak, Selangor, Negeri Sembilan states	265	105	39.6
2	Mar-1999	Singapore	Singapore	11	1	9
3	Jan-Feb 2001	India	Siliguri	66	45	68.2
4	Apr-May 2001	Bangladesh	Meherpur	13	9	69.2
5	Jan 2003	Bangladesh	Naogaon	12	8	66.7
6	Jan-Apr 2004	Bangladesh	Rajbari, Faridpur	67	50	74.6
7	Jan-Mar 2005	Bangladesh	Tangail	12	11	91.7
8	Jan-Apr 2007	Bangladesh	Kushtia, Naogaon, Natore, Pabna, Thakurgaon	18	9	50
9	Apr 2007	India	Nadia	5	5	100
10	Feb-Apr 2008	Bangladesh	Manikganj, Rajbari	11	9	81.8
11	Jan 2009	Bangladesh	Gaibandha, Nilphamari, Rangpur, Rajbari	4	1	25
12	Feb-Mar 2010	Bangladesh	Faridpur, Gopalganj, Kurigram, Rajbari	17	15	88.2
13	Jan-Feb 2011	Bangladesh	Comilla, Dinajpur, Faridpur, Lalmohirhat, Nilphamari,	44	40	90.9
14	Jan 2012	Bangladesh	Joypurhat	12	10	83.3
15	Jan-Apr 2013	Bangladesh	Gaibandha, Manikganj, Naogaon, Natore, Pabna,	24	21	87.5
16	Jan-Feb 2014	Bangladesh	13 districts	18	9	50
17	Mar-May 2014	Philippines	Philippines	17	9	52.9
18	Jan-Feb 2015	Bangladesh	Faridpur, Magura, Naogaon, Nilphamari, Ponchoghor, Rajbari	9	6	66.7
19	2018 May	India	Kozhikode and Malappuram	18	17	94.4
	Total			643	380	59

2.2 ETIOLOGY

Nipah virus infection is caused by nipah virus. It is an emerging virus that can cause severe respiratory illness and deadly encephalitis in humans.[47]

Due to its high pathogenicity, Biosafety level-4 containment is required to work with live NiV in laboratories.[48]

Among Paramyxoviruses, henipaviruses are characterized by a wider host range and a larger genome[12], when compared to the other members of the family, such as measles virus and canine distemper virus, showing generally a narrow host range and genetically stable with an almost uniform genome size shared by all members of Paramyxovirinae.[9]

As other animal Paramyxovirus, the virus is inactivated by 60°C for 60 minutes. It is stable between pH 4.0 and 10.0.

Nipah virus can survive for up to 3 days in some fruit juices or mango fruit, and for at least 7 days in artificial date palm sap (13% sucrose and 0.21% BSA in water, pH 7.0) kept at 22° C. It survives for long periods in favourable conditions, for days in fruit bat urine. It is susceptible to common soaps and disinfectants. Lipid solvents, such as alcohol and ether, and sodium hypochlorite solutions were used effectively in outbreaks for disinfection.[49]

2.2.1 Structure of Nipah virus (NiV)

Nipah is an envelope, single-stranded, nonsegmented, negative-sense RNA molecule of 18,246 nucleotides (nt) in NiV-MY and 18,252 nt in a NiV-BD.[5]

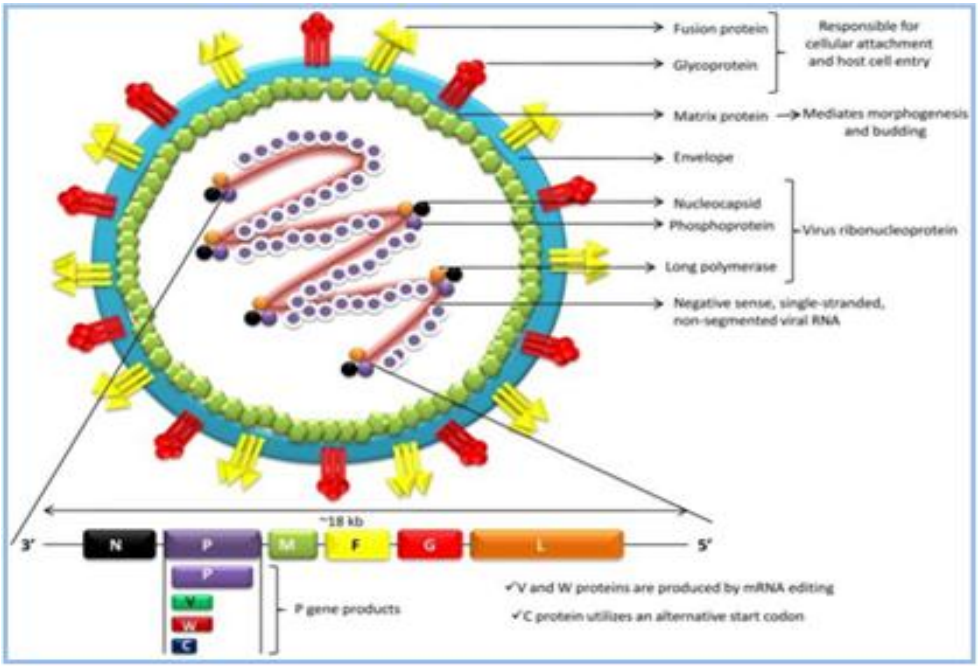

Fig 2.2.1 Structure of Nipah Virus.

It includes six genes corresponding to the nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G), and large protein (L). The P gene also encodes accessory proteins C, V, and W, which are synthesized by translation from another initiation site or by insertion of a G nucleotide.[6]

The N, P and L attached to the viral RNA forming the virus ribonucleoprotein (vRNP). The attachment (G) glycoprotein which binds the ephrin receptors, and the fusion (F) glycoprotein which drives virus-host cell membrane fusion, are the two membrane-anchored envelope

glycoproteins responsible for host cell infection by NiV.[9]

The virus M protein mediates morphogenesis and budding. Antibody to the G protein is essential for neutralization of the NiV infectivity.[102]

Virions are pleomorphic, ranging in size from 40 to 600 nm in diameter.[12]

NiV does not have the hemagglutinin and neuraminidase properties as commonly found in many Paramyxoviruses.[20]

2.3 TRANSMISSION

NiV is a zoonotic virus (a virus transmitted from animals to humans). Fruit bats in the genus Pteropus are the main reservoir of NiV.[50,51] Infected bats have not been reported to show any symptoms of the disease.

From bats, the virus has crossed its species-barrier frequently to several other species including man through spilled over transmission. Transmission of NiV to man occurs mainly in places where man, pigs and bats come in close proximity.[33]

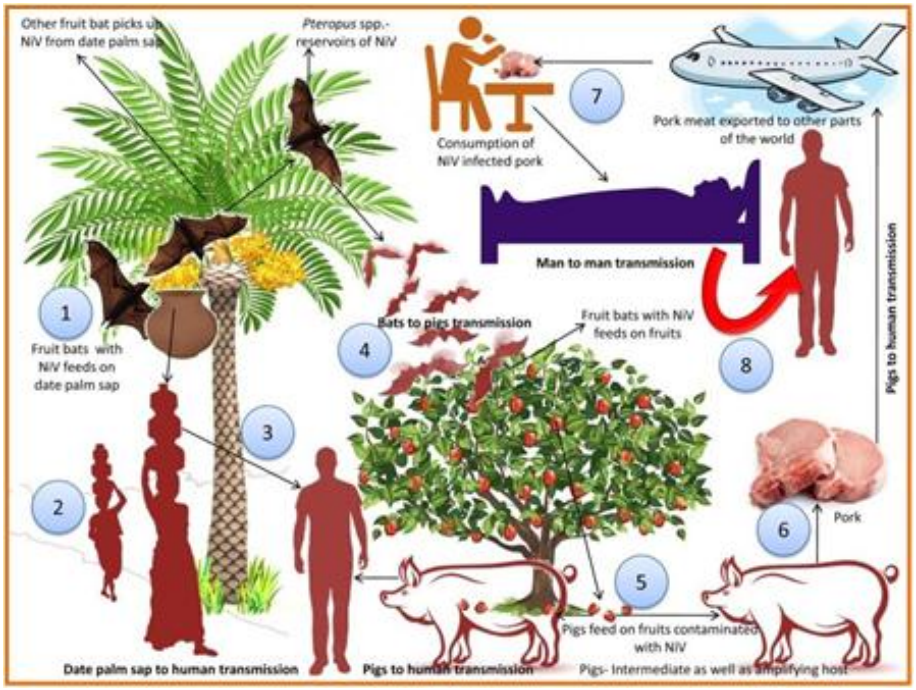

Fig 2.3 Transmission of Nipah Virus.

2.3.1 NiV Transmission in Malaysia, Singapore

NiV infected pigs were observed as main source for human infections (92%) during Malaysia and Singapore outbreaks.[36]

NiV outbreak in Malaysia occurred during 1998–1999 due to the spillage of NiV from bats to pigs after consuming half eaten-fruits by bats.[52]

Fig 2.3.1 Bat eaten fruits: A mode of transmission

Transmission to humans is thought to have occurred via respiratory droplets, contact with throat or nasal secretions from the pigs, or contact with the tissue of a sick animal. Infection also spread to pig handlers in Singapore, as pigs were imported from Malaysia.[52]

The findings in the pig‘s respiratory system could explain the severe pulmonary symptoms in these animals and provide support for the suggestion that aerosol spread of NiV from pig to human represents an important mode of transmission.[53]

Urine exposure may also be associated with transmission as NiV antigen has been demonstrated in the renal tubules of pigs and a concurrent outbreak of NiV among abbatoir workers in Singapore also showed the associatedness of infected pig urine and exposure to the workers.[28,54]

Control and experimental study prove that oral and respiratory as main routes of NiV transmission.[55,56]

2.3.2 NiV Transmission in Bangladesh

While the outbreak in Malaysia had progressed from the natural host (fruit bats), to amplification host (livestock) and finally to humans, in Bangladesh no amplification host was needed.[57]

Epidemiological investigations in Bangladesh have identified three pathways of transmission of NiV from bats to people.

The most frequently route is ingestion of fresh date palm sap.

Infrared camera studies confirm that P. giganteus bats frequently visit date palm sap trees and lick the sap during collection.[59] NiV can survive for days on sugar rich solutions such as fruit pulp.[60]

A second route of transmission for NiV from bats to people in Bangladesh is via domestic animals. Fruit bats commonly drop partially-eaten saliva-laden fruit. Domestic animals in Bangladesh forage for such food. Date palm sap that is contaminated with bat feces and so is unfit for human consumption is also occasionally fed to domestic animals. The domestic animals may become infected with NiV, and shed the virus to other animals, including humans.[61]

Third, some people may come into direct contact with NiV infected bat secretions. In the Goalando outbreak in 2004 persons who climbed trees were more likely to develop NiV infection than controls (odds ratio 8.2, 95% CI 1.3, undefined).[28]

Large number of Bangladesh and india Nipah outbreaks resulted from person-to- person transmission through close contact with people's secretions and excretions.

The clearest illustration of person-to-person transmission occurred during the Faridpur outbreak in 2004, where the chain of transmission eventually involved 5 generations and affected 34 people.[33] This is most commonly seen in the family and caregivers of Nipah virus-infected patients.[62]

2.3.3 NiV Transmission in India

In India, in a bat sample survey, NiV RNA was detected in a liver homogenate of P. giganteus captured in Myanaguri, West Bengal.[63]

In Siliguri, India, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors.[64]

2.4 PATHOGENESIS

The virus enters its host through the oro-nasal route and causes infection.

After entering into respiratory system virus is seen in bronchi and alveoli envading the epithelium of bronchi and type II pneumocytes which are supposed to be the main targets of virus. During this phase virus acts as potential source of infection for human to human transmission.

Virus enters the epithelial cells through ephrin-B2 and ephrin-B3 receptors which are the highly conserved proteins.

Ephrin-B2 and B3 are type I transmembrane proteins. They belong to the ephrin family of receptor tyrosine kinases consisting of 330 amino acids encoded on human chromosome 13 and 17, respectively.[65,66]

NiV contains two membrane anchored glycoproteins within their envelope, the receptor-binding G glycoprotein (G) and the fusion (F) glycoprotein.

NiV-G recognizes and attaches the virus to Ephrin-B2 receptors within the host cell membrane.[67]

This binding causes conformational changes in NiV-G contribute to the ―triggering‖ of the fusion protein F, leading to the fusion between viral and cellular membranes, resulting in the release of the viral ribonucleocapsid into the cytoplasm.[68]

After entering into the cytoplasm,the negative sense viral RNA is transcribed to mRNA which acts as a template for more negative sense viral RNA.

The viral RNA is used to make the necessary proteins (N,P,M,F,G,L,C,V,W) which congregate near the cell membrane. Once all the necessary proteins are assembled a new viral cell will bud off and infect other hosts. The new viral cells are able to fuse together and create a huge multinucleated cell called syncytia.[103]

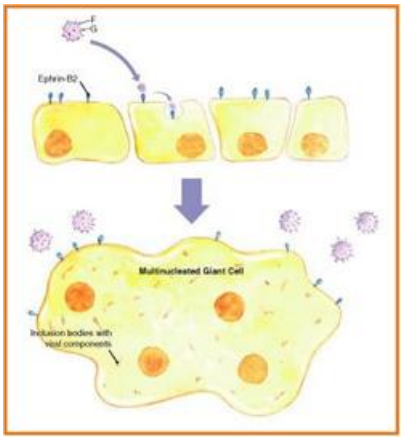

Fig 2.4 HeV and NiV interact with Ephrin-B2 on endothelial cells, leading to the formation of multinucleated giant cells.

From the respiratory epithelium, the virus is spread to the endothelial cells of the lungs causing vasculitis of small vessels. Later on, the virus gains entry into the blood stream followed by dissemination, either freely or in host leukocyte bound form.

Apart from lungs, spleen and kidneys along with brain may act as target organs leading to multiple organ failure.[69] There is development of lethal infection in hamsters when leukocytes loaded with NiV are passively transferred.[70]

- **Entry into the CNS**

Entry into the CNS is thought to occur through two distinct pathways: anterogradely via the **olfactory nerve** and/or via the **hematogenous route** through the choroid plexus and cerebral blood vessels.[71]

Henipavirus (HNV) infection of the CNS and the development of neurological signs are associated with the disruption of the blood-brain barrier (BBB) and expression of TNF- α and IL-1β.[69]

TNF- α and IL-1β are proinflammatory cytokines play an important role in increasing the permeability of BBB. Source of TNF- α and IL-1β remain unknown NiV subsequently infects neurons extending through the cribriform plate into the olfactory bulb, providing a direct route entry into the CNS.

NiV then spreads to the olfactory tubercle and throughout the ventral cortex.[72]

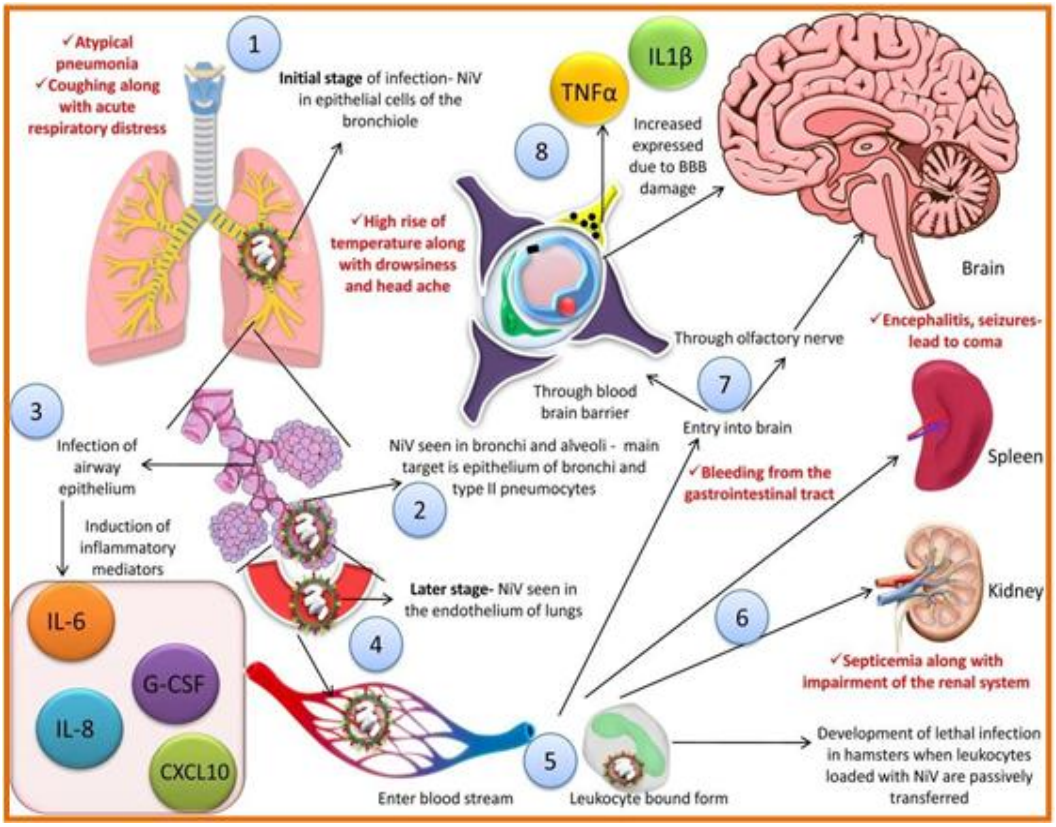

Fig 2.4 Pathogenesis of NiV.

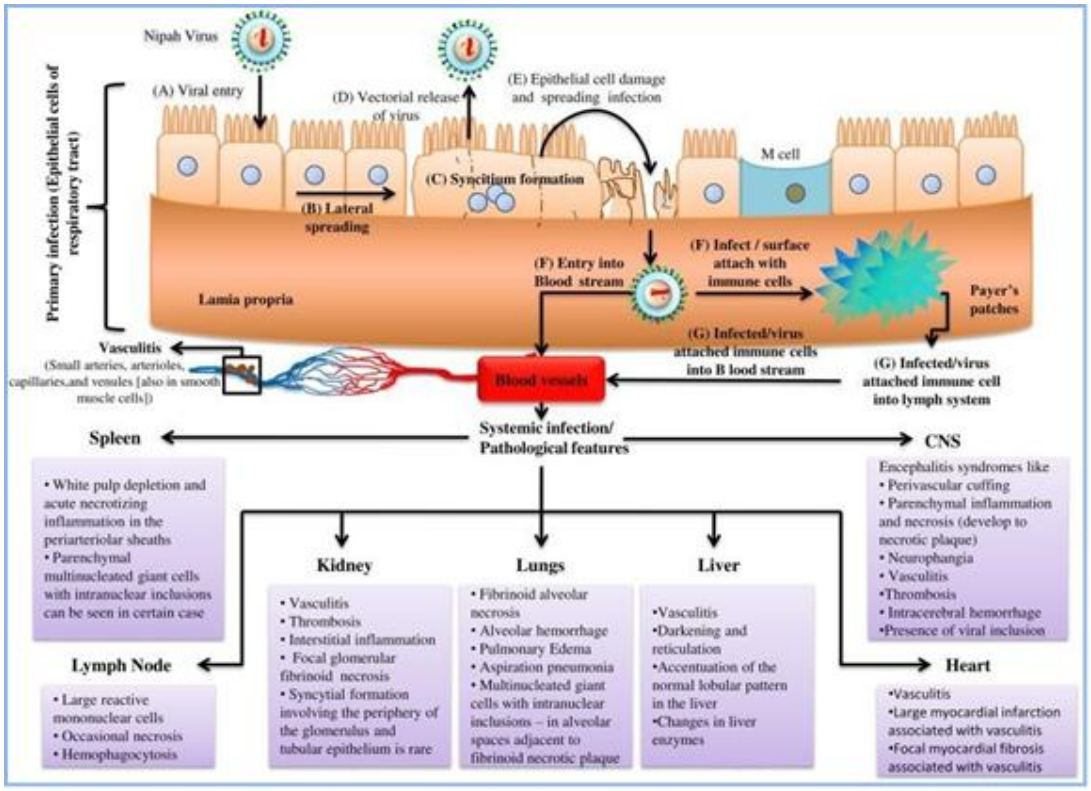

Fig 2.4. Pathophysiology of Nipah Virus infection.

2.5 CLINICAL SIGNS AND SYMPTOMS

Human infections can range from asymptomatic infection, acute respiratory infection (mild, severe), to fatal encephalitis.

The symptoms start to appear after 5–14 days from exposure.[73]

Fever, headache, dizziness, myalgia, vomiting and loose stools have been documented as non-specific prodromal symptoms in various outbreaks of Nipah.[29]

At the early stage, NiV infection typically presents as febrile encephalitis or pneumonia, and can be difficult to distinguish from other febrile illnesses. Respiratory distress was a hallmark in approximately 20% of cases in the Malaysia–Singapore outbreak and 70% of cases in Bangladesh–India.[74]

Encephalitis follows and those infected may exhibit drowsiness, disorientation, mental confusion, altered consciousness, and seizures that can progress, within 24-48 hours, to coma and eventually death.

Some patients have a respiratory illness during the early part of their infections, and half of the patients showing severe neurological signs showed also pulmonary signs.[73]

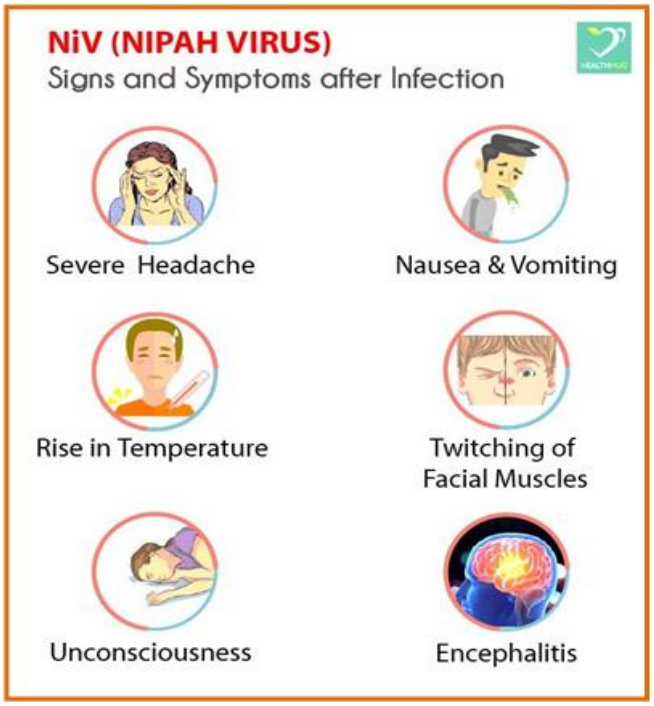

Fig 2.5 Clinical signs and symptoms of Nipah Virus.

Most people who survive acute encephalitis make a full recovery, but long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality changes. A small number of people who recover subsequently relapse or develop delayed onset encephalitis.

2.6 DIAGNOSIS

Nipah virus is classified internationally as a biosecurity level (BSL) 4 agent. In India, testing facility is available at National Institute of Virology (NIV), Pune.

Procedures for the laboratory diagnosis of Nipah virus infections include serology, histopathology, immunohistochemistry, electron microscopy, nucleic acid amplification test (NAAT) like polymerase chain reaction (PCR) sequencing, and virus isolation.

The recommended initial screening tests are ELISA serology and immunohistochemistry, neither of which amplify infectious virus, and so are safer tests in the laboratory.[75]

2.6.1 Nucleic Acid Amplification Test (NAAT)

2.6.1.1 Polymerase Chain Reaction (PCR)

NAATs such as PCR are often the preferred method for detection of active viral infection as they are highly sensitive. Further, these tests can lose sensitivity if the viral genome undergoes significant genetic mutation or if new strains differ in the regions of probe design.

Reverse transcription Polymerase Chain Reaction (RT-PCRs) can be used for detection of viral sequences in fixed or fresh tissue or CSF specimens Reverse-transcriptase PCR (RT-PCR) tests for NiV have targeted the conserved N, M or P genome segments.During the early stage of illness virus isolation and reverse transcriptase polymerase chain reaction assay (RT PCR) from throat and nasal swabs, cerebrospinal fluid (CSF), urine, and blood is recommended.[76]

Several types of PCR tests for NiV have been developed, including conventional RT- PCR, nested RT-PCR and real-time RT-PCR (also known as quantitative PCR or qPCR). Real-time PCR has been shown to be 1000 times more sensitive as conventional PCR, and is now used almost exclusively.[77]

2.6.1.2 Sequencing

Next-generation sequencing and deep sequencing enable a direct read of the viral genome,

allowing virus and clade identification without prior knowledge of the composition.As this approach is Complex and expensive, this is not practical for screening larger numbers of samples in a diagnostic context.[78]

2.6.2. Serological assays

Serological tests can directly detect NiV antigens, as well as IgM and IgG antibodies raised against NiV antigens.[74]

During the convalescent phase, antibody detection by enzyme linked immunosorbent assay (ELISA-IgG and IgM) from serum or CSF may be used.[29]

IgM ELISA is typically the first-line NiV serological diagnostic test, followed by serum neutralisation or PCR as a confirmatory test.[79,80,81]

Antigen and IgM tests can be used to detect active infection; detection of anti-NiV IgM in serum peaks after 9 days of illness (based on hospital admittance) and can persist for at least 3 months. Since IgG can persist long after convalescence, IgG tests are primarily used for epidemiological studies and surveillance; detection of anti-NiV IgG peaks after 17 days of illness and can persist for more than 8 months.[82] Its use is limited to BSL4 laboratories.

2.6.3. Immunohistochemistry

Immunohistochemistry is the safest tests. It is performed on formalin-fixed tissues and highly recommended for initial NiV virus diagnosis, as the primary pathology occurs in the vascular endothelium, viral antigen can be detected in a range of tissues.

In fatal cases, immunohistochemistry on tissues collected during autopsy may be the only way to confirm a diagnosis.[62]

Samples should be transported at 4°C and processed as early as possible. During the early stage of illness - virus isolation and reverse transcriptase polymerase chain reaction assay (RT PCR) from throat and nasal swabs, cerebrospinal fluid (CSF), urine, and blood is recommended.[76] During the convalescent phase, antibody detection by enzyme linked immunosorbent assay (ELISA-IgG and IgM) from serum or CSF may be used.[29]

- Advanced diffusion weighted (DW) magnetic resonance imaging (MRI) of the brain can give useful radiological evidence of Nipah encephalitis.

Lim et al. suggested that MRI pattern may be useful in differentiating Nipah from its closely differential related Japanese encephalitis/other encephalitis in most cases.It helps in deciding treatment and post exposure prophylaxis.[82]

2.7 PREVENTION

Prevention of Nipah virus infection is important since there is no effective treatment available for the disease.[83]

Bat-borne viruses carry undeniable risks to the health of human beings and animals, and there is growing recognition of the need for a _One Health' approach to understand their frequently complex spill-over routes.[84]

If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals with close supervision of burial or incineration of carcasses may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease.[3]

As Nipah virus outbreaks have involved pigs and/or fruit bats, establishing an animal health/wildlife surveillance system, using a One Health approach, to detect Nipah cases is essential in providing early warning for veterinary and human public health authorities.[3]

Fig 2.7 Doctors and relatives wearing protective gear carrying the body of a victim, who died due to Nipah virus, during his funeral at a burial ground in Kozhikode.

- **Reducing the risk of infection in people**

In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce

exposure to the Nipah virus.[3]

➢ **Reducing the risk of bat-to-human transmission**

Measures should be taken to avoid bat access to date palm sap and other fresh food products. Keeping bats away from sap collection sites with protective coverings (such as bamboo sap skirts and lime) may be helpful.[3]

Avoid drinking palm sap in bat dwelling places. If you want to drink it, boil it once so that the virus is removed.[3]

Fruits or vegetables should be thoroughly washed and cleaned properly in order to remove bat dropping or feces from it. Avoid consumption of half eaten fruits A physical barrier like net or a face mask should be kept around while rearing animals like piglets to prevent any direct contact. While rearing animals, make sure that you keep the bats away from the rest. Since bats are the primary carrier or this infection, bats must not be allowed to come near the other animals. Create a physical barrier so that bats cannot enter the place where other animals are kept.[3]

➢ **Reducing the risk of animal-to-human transmission**

Gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures.

There is a need to inspect all the imported livestock at the point of origin and when they arrive.[75]

All the facilities for their slaughter need to be maintained at the highest level of hygiene possible.[75]

As much as possible, people should avoid being in contact with infected pigs. In endemic areas, when establishing new pig farms, considerations should be given to presence of fruit bats in the area and in general, pig feed and pig shed should be protected against bats when feasible.

Farm animals should not be allowed to eat fruits exposed to bats.

➢ **Reducing the risk of human-to-human transmission**

Close unprotected physical contact with Nipah virus-infected people should be avoided.

Regular hand washing with soap and water or alcohol based hand rub should be carried out after caring for or visiting sick people.[3]

Wearing of personal protective equipment (PPE) when performing an aerosol generating procedure or a patient examination. Highest level of protection is recommended for Nipah Infections in health care workers (HCWs) with SARS or Ebola during the respective outbreaks were very commonly attributed to improper PPE removal or doffing.[85,86] The patient must keep themselves hydrated.

Standard infection control practices should be enforced to prevent nosocomial infections.[83] As the vaccine against NiV is still in the preclinical stage and no other proper treatment options are available, the main aim of NiV management should focus on prevention. It is vital to properly educate the at-risk populations about the means of transmission of the virus.[87]

Fig 2.7 Preventive measures for nipah virus.

2.8 TREATMENT

Currently there is no known treatment or vaccine available for either people or animals. Treatment is limited to supportive care and syndromic management of acute encephalitis syndrome.[88]

However Ribavirin, an antiviral may have a role in reducing mortality among patients with encephalitis caused by Nipah virus disease.[89] Treatment is limited to supportive care

2.8.1 Monoclonal antibody m102.4

Neutralizing human monoclonal antibody has been found to be effective in a non- human primate model.[90]

Monoclonal antibody, m102.4 targets the ephrin-B2 and ephrin-B3 receptor binding domain of the Henipavirus G envelope glycoprotein. It was effective in protecting ferrets from lethal NiV challenge.[91]

In another animal study, 12 african green monkeys were given m102.4.All treated animals remained clinically healthy, whereas the control animal rapidly succumbed to disease on day 8 after infection.[90]

Use of anti-G and anti-F monoclonal antibodies in an emergency setting is approved in India.[92]

2.8.2. Ribavirin

Ribavirin, also known as **tribavirin**, is an antiviral medication used to treat RSV infection, hepatitis C and some viral hemorrhagic fevers.

Mechanism of Action: It is a guanosine (ribonucleic) analog used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor. Ribavirin is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form, it interferes with RNA metabolism required for viral replication.

It has been noticed in the recent outbreak in Kerala in South India that the antiviral drug ribavirin could be explored as anti-NiV agent.

As per NiV study, Ribavirin helps reduce viremia in patients infected with Nipah virus but there has been no proof yet that it is an effective treatment for Nipah.

The doctors in Malaysia who have administered Ribavirin in Nipah-infected patients have also confirmed its promising effects in slowing the virus from spreading all over the body.

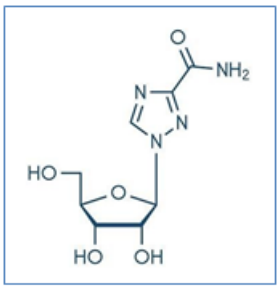

Fig 2.8.2 Structure of Ribavirin.

For best results, the doctors advise that the treatment should be given within 2-3 days after an individual shows symptoms of Nipah infection.[3]

The dosage of ribavirin in Nipah virus has not been defined but treatment can be initiated in the lines of that suggested by WHO for Lassa fever with a loading dose of 30 mg/kg for children and 2,000 mg/kg for adults, followed by 10 days of therapy (4 g in divided doses for first four days and 2 g in divided doses for next six days).[3]

Ribavirin is not bound to plasma proteins.[94] Ribavirin was found to cross the blood- brain barrier following oral administration with a mean CSF/plasma ratio of 0.7.[95]

Adverse drug reactions[93]

Neutropenia (8% to 40%),

Anemia (11% to 35%; children & adolescents: 11%)

Lymphocytopenia (12% to 14%).

2.8.3. Favipiravir

Favipiravir has demonstrated efficacy against a broad spectrum of RNA viruses, including members of the Paramyxoviridae, Filoviridae, Arenaviridae families, and the Bunyavirales order.[96]

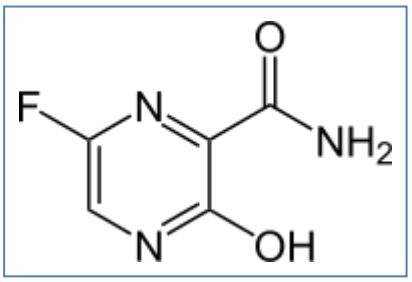

Fig 2.8.3 Structure of Favipiravir.

Mechanism of action: Selective inhibition of viral RNA-dependent RNA polymerase. In vitro, favipiravir inhibited Nipah and Hendra virus replication and transcription at micromolar concentrations.[96]

Twice daily oral or once daily subcutaneous administration of favipiravir for 14 days fully protected hamsters challenged with a lethal dose of Nipah virus.[96]

2.8.4. Remdesivir (GS-5734)

Remdesivir (GS-5734) is a broad-acting antiviral nucleotide prodrug.

***Mechanism of action*:** Remdesivir is a prodrug that metabolizes into its active form GS-441524. An adenosine nucleotide analog, GS-441524 interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.

The efficacy of remdesivir (GS-5734) was tested against Nipah virus Bangladesh genotype in African green monkeys. Animals were infected with a lethal dose of Nipah virus, and a once-daily intravenous remdesivir treatment was initiated 24 hours later and continued for 12 consecutive days.

The team observed the animals for 92 days after infection, taking clinical samples 14 times during that span. The long period of observation allowed scientists adequate time to monitor the central nervous system for disease, which can be slow to develop when caused by Nipah virus. Mild respiratory signs were observed in two of four treated animals, whereas all control animals developed severe respiratory disease signs. In contrast to control animals, which all succumbed to the infection, all remsdesivir-treated animals survived the lethal challenge.[97]

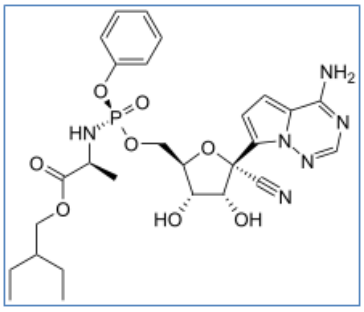

Fig 2.8.4. Structure of Remdesivir (GS-5734)

2.8.5 Nanoparticles (NPs) in inhibiting NiV Infection.

Major limitations of synthetics drug is their lack of target specificity and probability of host cell toxicity.

Due to the consistent change in their genome these viruses would get resistance to the conventional drugs which are unidirectional and have no specific target.

These limitations could be mitigated by finding a novel therapy with multiple pathways and biomarkers f**o**r the target oriented action.[106]

Taking into consideration, the severity of the infection and imperative necessity for a novel multidirectional, target specific and, non-toxic nature; the tunable nanotechnology based approaches seems to be a promising alternative.[106]

ADVANTAGES[105]

1. They have the capacity to channelize through translucently breachable blood–brain barrier (BBB) and blood–air barrier (BAB),
2. Tunability and
3. Targeted control discharge.

Numerous intermediate molecules have found to be associated with ESCRT pathway; targeting conserved intermediate molecules or their precursor might be a novel strategy to eliminate the NiV. Further the ligands or receptors with a binding efficiency with viral intermediate molecules could be further enhanced by their amalgamation with nanotechnology.[104]

The versatile mode of viral inhibition primarily depends on the type and form of NPs used. Therefore to understand the antiviral activity of NPs a general overview about different types and forms of NPs/ nano-based systems is a necessity. Nano-based antiviral agents extend from simple inorganic NPs to complex organic and hybrid nanosystems.[106]

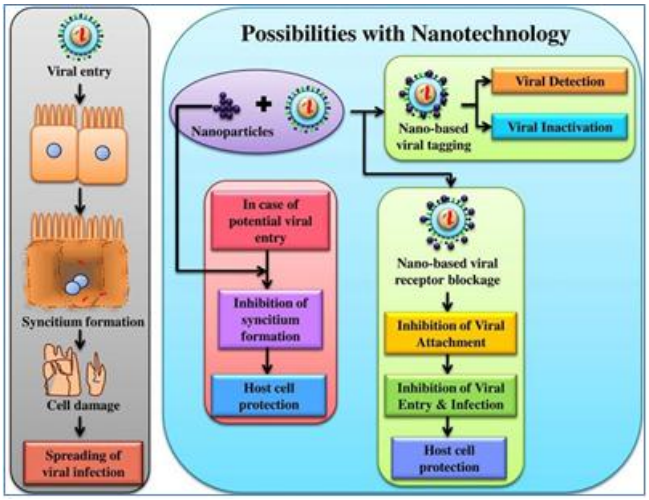

Fig 2.8.5: Nanoparticle based detection and inactivation NiV infection specifically through targeted tagging or by blocking viral surface proteins.

2.9. VACCINES

Hendra virus G glycoprotein elicits a cross protective immune respone in ferrets against both nipah virus and hendra virus. Ferrets were vaccinated with 4, 20 or 100 µg HeVsG.

Ferrets exposed to Nipah virus 20 days post vaccination remained clinically healthy. Virus or viral genome was not detected in any tissues or fluids of the vaccinated ferrets; lesions and antigen were not identified on immunohistological examination of tissues; and there was no increase in antibody titre during the observation period, consistent with failure of virus replication.[98]

Virus vector-based recombinant vaccines have also been developed. These recombinant viruses express the F or G glycoproteins on their surface.[99,100]

A recombinant measles virus (rMV) vaccine expressing NiV envelope glycoproteins (rMV-HL-G and rMV-Ed-G)was used. Vaccinated hamsters were completely protected against NiV challenge, while the mortality of unvaccinated control hamsters was 90%.[101]

All these approaches have produced complete protection against oro-nasal NiV challenge after a single dose in various animal models.[17]

3. CONCLUSION

NiV has emerged as a deadly zoonotic disease. Even after its two decades of emergence NiV continuous to casue annual outbreaks in southeast Asia.

The virus can cause large outbreaks if its get adapted to human to human transmission.

Extensive research has been going on to understand NiV pathogenesis and its subsequent transmission which is important to develop NiV vaccines and their clinical trials in human.

By understanding NiV pathogenesis, therapeutics can be developed which will aid in the treatment of infected subjects.

The role of monoclonal antibodies and drugs like ribavirin, Favipiravir and remdesivir has to be clearly established with the help of properly designed clinical trials.

There is a need for educating the common people about personal and food hygiene.

For the prevention of NiV and other zoonosis there is the need to inspect all the imported livestock at the point of origin and where they arrive.

Habitat destruction and climate change causes increase in contact between bats and humans which may leads to more zoonotic transmission events in the future.

Educating people regarding the transmission should be number one priority in combating NiV outbreaks.

There is need of developing communication between veterinary and medical services concerning this disease through platforms like Global Outbreak Alert and Response Network (GOARN) held especially after the outbreaks in Bangladesh and India the common people should be educated about food hygiene as well as hygiene at personal level.

A better understanding of bat ecology and the causes of spill-over events, and strengthening of surveillance systems to prevent outbreaks is required to curb the threat posed by NiV.

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