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Therapeutics of Nipha virus: Recent Development and Advances

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ABSTRACT

The Nipah virus (NiV) is a virus with high fatality rate causes mortality. Historically afflicted many developing countries. Several countries with developing economies, including Future outbreaks are likely to threaten Thailand, Cambodia & Madagascar, according to Centres for Disease Control & Prevention (CDC). Little has been accomplished in nearly 20 years since 1st case of NiV was reported in terms of developing a treatment & vaccine. Since many underdeveloped countries lack capacity to combat epidemic, it is imperative to properly educate health systems. An epi-demiological back-drop, comprehension of how this lethal virus is transmitted, how it appears & methods of diagnosis & prevention are among aims of this review. The emergence of novel viruses & diversity of viruses are occurring at an alarming rate. Due to the sudden emergence of the (NiV), serious concerns have been raised over its immediate management using conventional medical treatments & testing processes. When (NiV) enters host cell via a cell surface receptor, syncytium is created. The virus is discharged into circulation & spreads to other organs as syncytium gradually breaks down. By targeted tagging & blocking action of viral surface proteins, NiV infection can be selectively detected & neutralised with aid of nanotechnology. Creating a targeted nano-system against these expressed pro-teins may also aid in preventing spread of viral infection because NiV-infected cells also produce these viral surface proteins, which aid in creation of the syncytium.

Keywords: *Nipah virus, Virus infection, Diagnostics, Antiviral Virucide*

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Introduction: The enveloped, non-segmented Nipah virus (NiV), as well as the Hendra (HeV), Cedar (CedPV), and numerous other unnamed henipa-viruses found in Africa, are

all members of Henipa-viruses genus of the Paramyxoviridae family. In 2020, Loomis et al.

It is obvious that nano-science will keep growing for millennia to come thanks to the adaptive breakthroughs in nanotechnology during the last ten years. Despite expendability & flexibility of Nano-technological applications, the intriguing experimental biomedical usage and their considerable commercialization are far apart. It's crucial to prioritise their application in biological science in order close gap. Additionally, due to development of resistance, conventional thera-pies are becoming less and less effective, especially in cases of viral infections (Kerry et al., 2019).

The (NiV) enters host cell via its cell sur-face recep-tor, which results in the formation of syncytium. The virus is discharged into the circulation and spreads to other organs as the syncytium gradually breaks down. Nipah virus spillovers have happened less frequently, but overall fatality rates have noticeably gone up by between 75 to 100%. It is important to remember that during outbreaks, direct human-to-human transmission of the Nipah virus from bats to humans has also been observed in Bangladesh and India.The epidemiological data about the spread of Nipah & Hendra viruses among people since both viruses' appearance & identification have recently undergone a detailed assessment & summary. (2013) (Broder et al.).

The Henipa-viruses genus, Para-myxoviridae subfamily, Paramyxoviridae family, order Mononegavirales, (NiV) is a para-myxo-virus that can cause fatal en-cephalitis & serious respiratory diseases in humans. It is a segment-free, encapsulated, single-stranded, negative virus with helical-symmetric sense RNA. Six genes are sequentially placed in the RNA genome from 3' to 5' position: long polymerase (G), fusion glycol-protein (F), phosphoprotein (P), matrix (M), & nucleo-capsid (N), (L). The N, P & L make up the virus ribo-nucleoprotein (vRNP), which is joined to viral RNA. The host-cell invasion that follows virion's cellular attachment is made possible by F & G-proteins. It has been demonstrated that mono-meric ephrin-B2 binding causes the NiV G-protein to go through allosteric changes, allowing for full acti-vation & receptor-activated viral entry in host cells. The G-protein of NiV supports changes in G -protein that result in refolding of F-protein via binding to ephrin-B2/3 receptors inside host. Recent studies have revealed The nucleolus DNA-damage response path-way is specifically targeted by viral control of host cell machinery, which leads to an increase in production of henipa-viruses (Hendra & Nipah viruses).

The NiV G protein undergoes allosteric changes as a result of mono-meric ephrinB2

binding, which have been demonstrated to facilitate full receptor-activated viral entry into host cells. According to recent studies, henipa-viruses (Hendra & Nipah viruses) are produced more readily when nucleolar Treacle protein is inhibited, which targets the nucleolar DNA-damage response (DDR) pathway 2019 (Singh et al.).

Pigs infected with NiV display more severe respiratory symptoms than do humans. Ephrin-B2, a NiV entry receptor whose expression levels varied between cells from different donors, is expressed at high concentrations in human airway epithelium. a quick NiV spread. (2016) Sauerhering et al. After NiV infection, human respiratory epithelial cells produce more IFN. NiV replication in humans can be sped up by variations in its receptor expression (2017) Sauerhering et al.

The host targets of the virus are PRP19 complex & micro-RNA processing machinery. Both expression of genesis & p53 control are altered by virus's W protein. Affinity purification and mass spectrometry have been used to determine relationship b/w human & NiV pro-teins. (2017) Martinez-Gil et al.

VLPs composed of human-derived proteins M, G & F have been described using liquid chromatography & mass spectrometry.

Method:

We reviewed studies on NiV that have been written about in MEDLINE and Google Scholar papers. Included in the key phrases are "Nipah virus disease manifestation" and "Nipah virus disease prevention." Only publications made between January 1, 1998, and June 30, 2018, were included in the search. Before gathering to discuss the papers, each author individually reviewed them. It was mentioned that the terms "Nipah virus," "epidemiology of Nipah virus," "transmission of Nipah virus," and "clinical" were all related. "Nipah" & "Hendra, "henipaviruses," along with addi-tional MeSH terms: "Nipah virus infection," "Innate immune Nipah virus," "Adaptive immune Nipah virus," "B cells Nipah virus," "T cells Nipah virus," "Epi-demiology Nipah All literature reviews, first publications, and case reports that explored the genesis, mode of transmission, clinical manifestation, pathology, and immunological responses of the NiV were included up until March 31, 2022. These articles also contained extra cross-references. Epi-demiological reports from WHO & other public health organisations were also assessed.

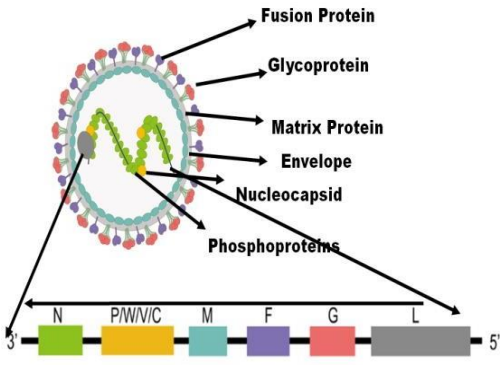

Fig: Nipah Virus

Structure of Nipah Virus:

The large protein & RNA poly-merase protein (L), fusion protein (F), attachment glycol-protein (G) & nucleoprotein (N) are among 6 structural proteins encoded by 18.2 kb negative-sense single-stranded RNA that makes up the NIV genome.

Transmission of Nipah Virus:

For several high-risk diseases like the Nipah, rabies & Marburg viruses, bats act as reservoir hosts. These viruses don't significantly affect the bat population's pathogenic makeup. 2014's Schountz. To fully understand the processes of pigs to people, pigs to bats & date palm sap to human NiV transmission, as well as viral circulation b/w fruit bats, pigs & humans, more in-depth research is needed. Fruit bats have been linked to numerous outbreaks & are a natural reservoir for the Nipah viruses. These bats, which originate from various geographical regions around the globe, have been somehow linked to the spread of the virus and the illness that goes along with it. The virus frequently transmits from bats to a range of other animals, including man, through spillover transmission. Less subsequent transfer from one individual to another has, however (Yadav et al., 2018).

Most places where pigs, people & bats congregate are also places where NiV is spread to people. On farms and in the vicinity of them, fruit-bearing trees are also grown for shade and pigs are raised for their economic value. Fruits entice petrous spp. bats, which operate as NiV reservoirs and spread the disease to people, pigs & other animals. The sickness is spread to people by the animals in one area of the world. As a result of transcontinental transportation of tainted pig meat to humans in other parts of world. The presence of fruit bats, pigs, fruit-bearing shrubs, date palms & humans in close proximity has been substantially implicated in the genesis & spread of novel fatal zoonotic viral diseases like Nipah.

Transmission from Person to Person:

Person-to-person transmission was the cause of several Nipah epidemics in Bangladesh. The greatest proof of NIV transmission from person to person came from pandemic in Faridpur in 2004. Four carers for index patient had diseases b/w 15 & 27 days after patient's initial illness: his mother, son, aunt, & a neighbour. The index patient's aunt received medical attention. Throughout her hospitalisation, a revered religious leader who resided in the neighbourhood & fell ill 13-days later was present. When spiritual advisor became gravely ill, several of his family members & adherents of his faith gathered at his home. 22 people who had contact with religious leader afterwards developed Nipah virus. One of these followers moved to his family's residence in a neighbouring hamlet because he was ill, where a friend & two

family members took care of him. These 3-attendants, along with the rickshaw driver who helped bring him to hospital all became ill as his health deteriorated. The transmission chain, which covered 5-generations, had an effect on 34 people in all [21] (Figure 2). Physical contact with a patient who was NiV-infected & later died was most important risk factor for contracting illness during pandemic (13.4; 95% CI, 2.0-89) (Luby et al., 2009).

Pathogenesis of NV:

NiV enters humans and other animal hosts through the nasal passages to infect its hosts. The lymphoid and respiratory tissues contain high quantities of viral antigens, and the respiratory epithelial cells are infected with the virus.2016 (Clayton et al.). With initial viremia, the virus spreads to several physiological organs while endothelial secondary replication occurs. NiV infection of host cells begins with viral G protein attaching to cellular ephrin-B2 & B3 receptors (2005) Bonaparte et al.

The virus then quickly spreads to spleen, kidneys, heart, liver, & other organs during 1st week of illness (2017) Mire et al.

Numerous cell types, including neurons, endothelial cells, & epithelial cells, have ephrin-B2 and -B3. Both of these cellular receptors are largely maintained because they are present in all animal species. According to Bossart et al. (2008), NiV is tissue- and species-specific. Extended NiV production had no cytopathogenic effects on smooth muscle cells. Together, the investigations suggested that NiV might have an unidentified entry receptor or a universal viral entrance mechanism. Furthermore, it has been hypothesised that NiV can enter the brain by way of circulating immune cells, notably monocytic cells and developing dendritic cells. It was established that these cells were NiV-permissive, but the virus was unable to successfully replicate there. But in a lab setting, NiV-infected immune cells bypassed blood-brain barrier & went after vulnerable, infected cells, simulating presence of localised lesions and neuronal infection in brains of NiV-infected individuals & animals 2019 (Liu et al.).

Clinical findings of Nipah virus disease:

Additionally possible are nausea & vomiting. One-third of individuals had meningismus. In 60% of instances, there were significant neurological symptoms & a sharp decline during the following 5-7-days. It has been determined that 20% of seizures are brought on by nipah encephalitis. Other neuro-logical symptoms were flexion & segmental myoclonus, among others. Chronic fatigue & regular sleepiness have also been reported by long-term survivors. (2007) Sejvar et al.

How is an illness caused by the Nipah virus:

Despite the fact that presence of NiV antibodies is the gold standard for diagnosis, Nipah has been classified as a disease with a biosafety grade, hence this approach is not used. Enzyme-linked immunoassay diagnostic tests have a high degree of specificity. Another possible method of investigation is polymerase chain reaction 2015 (Ong & Wong).

The autopsy results of 32 Malaysian epidemic victims showed vasculitis that resulted in extensive micro infarction. These individuals also displayed vasculitis lesions of heart, kidneys & respiratory tract. Medium-sized blood arteries were more likely to develop fibrinous necrosis & endothelial multinucleated syncytia 2015 (Ong & Wong).

MRI scans of NiV patients have revealed a number of tiny, asymmetric focal lesions in deep & sub-cortical white matter that are less than 5mm in size & devoid of oedema around them. (1999; Lim et al.).

Epidemiology of Nipha virus:

The epidemiology of NiV is not completely characterised since viral research needs a lab with a bio-safety level 4 (BSL-4) facilities. The NiV virus is thought to have its native animal reservoir in flying fox, also known as Pteropus fruit bat 2019 (Sharma et al.).

In 1998, NiV infection was discovered in Malaysians who had contact with the swine population. When Malaysian pig flesh was imported in March 1999, Singapore reported one mortality incidence from acute Nipah virus infection among 11 male abattoir workers (average age: 44). Increased serum IgM levels, specific encephalitis and pneumonia symptoms & characteristic MRI focal areas with increased White matter cortical signal strength were all present in the patients. Hallucinatory symptoms were noted in addition to abnormal laboratory findings like high CSF protein levels, low lymphocyte and platelet counts, & elevated aspartate amino transferees. After receiving intravenous acyclovir, eight of the patients recovered (1999; Patterson et al.).

The sickness can be transmitted to humans or animals using a variety of techniques. Due to several aspects, such as varied breeding practises and some dietary patterns, it is peculiar how different hosts' channels of transmission varies based on geography (Bruno et al., 2023).The constant close contact of people with pigs and their excrement creates biological promiscuity, which is unquestionably the main risk factor for transmission in this area.(2000) Parashar et al.

In first epidemic, 45 out of 66 infected people died (68.18%) in the Siliguri region, and in the second, 5 out of 5 infected people died (100%) in Nadia district, both of which were documented NiV outbreaks in humans in India in 2001 & 2007. It is noteworthy that locals in these regions do not frequently consume date sap for food. Patient Zero, who was never

identified, was admitted to district hospital in Siliguri in 2001 & infected 11 other patients there. The infection spread to 25 medical professionals & eight patients after these patients were taken to other hospitals. (2006) Chadha et al.

In India, every outbreak that has been documented so far has shown the capacity to spread from person to person.The viral NiV strains found in Bangladesh & India are about six nucleotides different from those found in Malaysia. This unexpected result of molecular-genetic analysis is noteworthy. (2011) Arankalle et al. Contrarily, there aren't any reports of the Hendra virus at moment that would be relevant to show that Equidae are contagious carriers of this illness.

India:

There were two major outbreaks in India: one in Siliguri, West Bengal, in July 2001, which led to 66 probable cases and 45 fatalities, and another in Nadia, West Bengal, in 2007, which produced five cases with a 100% mortality rate. Along Nipah belt in Bangladesh, these diseases first appeared. Kerala, a state in south on west coast that is geo-graphically separate from previously impacted regions, declared a NiV pandemic in the Kozhikode and Malappuram districts in May 2018.

The practise of consuming date palm sap is uncommon in this area. There were 17 fatalities & 18 confirmed cases as of June 1st, 2018.

All patients were of an age that was considered to be economically productive & there was no difference in gender. The index case in Siliguri in 2001 was never recognised, but after being admitted to hospital, it spread the infection to 11 additional people. These individuals disseminated the illness after being admitted to other hospitals, infecting 25 staff members & 8 visitors. The 2007 outbreak only affected one person who fell ill after ingesting alcohol, while everyone else, including one healthcare professional, contracted the illness via date palms. At least one medical professional additionally contracted the infection while working at a medical facility in the most recent pandemic in 2018, which occurred in 2018. Every pandemic in India has included person-to-person transmission. Despite the fact that there have only been three reported NiV outbreaks in India, the epidemiology is similar to that of Bangladesh, therefore definitive evidence is still lacking. 2019 (Aditi & Shariff)

Infection of Host Cells by Viruses:

Entry Mechanism:

The Nipah virus's (NiV) replication & genomic structure. The Nipah virus replication cycle (A).The viral genome is released after NiV enters a cell, starting transcription & allowing viral mRNA transcripts to

accumulate. The entire anti-genome produced by viral genome is also employed to reproduce NiV genome. The translation of viral pro-teins created from viral mRNA leads to virion production, encapsulation, and virus release. NiV qRT- PCR test schematic (B). The NiV qRT-PCR assay was created using intergenic region of NiV. The viral mRNA & viral proteins are produced in untranslated region of F gene. Schematic of the NiV qRT-PCR test (B). The 3' region of G-gene is target of intergenic region of NiV, which inhibits viral m-RNA transcripts from producing erroneous signals & inflating viral RNA levels.

Therapeutics and Vaccines:

Host and Immune Responses:

Antibody responses and immunological assessments of vaccination efficacy have always been connected. While purified antibodies from convalescent serum have been researched as anti-viral strategies against henipa-viruses, they may be equally effective when used in passive immunisation as Neutralizing antibodies are produced through vaccinations, which are anti-cipated to be highly specific & effective. Both NiV F & G-proteins are considered to be strong candidates for vaccines as well as significant NiV & HeV antigenic sites. The m102.4 neutralizer binds to the NiV G & neutralises it, preventing G from attaching to host cell receptor (2008) Zhu et al.

Another recent develop-ment in therapy of NiV sick-ness is the humanised mAb h5B3.1, which has cross-reactivity with targets of NiV F-protein. The antibody offers encouraging defence against NiV & HeV sickness in ferrets 2020 (Mire et al.).

The only human monoclonal anti-body that has successfully passed phase 1 human testing & been evaluated for NiV & HeV pro-tective investigations in AGM model is m102.4, nevertheless. Together, these studies showed that monoclonal antibody immunotherapy, which specifically targets viral glycol-proteins, can successfully treat NiV infection. This highlights significance of humoral response to NiV glycol-proteins as a protective strategy 2019 (Dang et al.).

One of primary medical defences against viral infection in humans is use of a safe and efficient medicine. Vaccination that is effective against viral illnesses. A protective mechanism brought on by vaccination mostly consists of neutralising anti-bodies. The viral F & G-proteins' primary anti-gen binding regions are in charge of neutralising antibodies for NiV.Therefore, if a vaccination can produce neutralising anti-bodies that are specific to these viral proteins, it will be effective against NiV. Different vaccination strategies have been developed & evaluated using animal models 2004 (Guillaume et al.).

Several anti-viral drugs were investigated for treatment of NiV. But just a few of them, such as ribavirin, remdesivir & favipiravir, have undergone tests in animal models. The first antiviral drug used to treat NiV was ribavirin 140 people with NiV infection died less frequently overall thanks to ribavirin treatment during Malaysian outbreak of 1998–1999 (Goh et al., 2000).

Remdesivir (Veklury), an alternative adenosine nucleoside anti-viral medication, has recently been studied in AGMs. Remdesivir is a NiV antiviral drug that may be beneficial because, compared to all untreated animals; just 2 of 4 mice that received it displayed moderate respiratory issues. (Lo et al., 2019).

Suffered from severe respiratory difficulties. During the 1999 NiV outbreak in Singapore, ceftriaxone and another antiviral, acyclovir (Zovirax), were administered to nine abattoir workers; eight of them made a full recovery (1999; Patterson et al.).

Acyclovir in vitro testing against NiV produced no results. Studies have shown that favipiravir, also known by brand name Avigan, & other medications block NiV virus from replicating in vitro (Rao & Srinivasan, 2021).

By producing IFN- & IFN- in hamsters, immuno-modulator ritatolimid (Ampligen) was found to be effective in reducing NiV proli-feration & provide pro-tection from viral infection. However, there is currently a dearth of in vitro & in vivo research that has been conducted, necessitating need for more thorough information on efficacy of anti-viral drugs that might be used to successfully treat NiV infection in humans (Liew & others, 2022).

Vaccines in Development:

Several as we learn more about the molecular biology of NiV, research on vaccinations is being conducted. Early studies revealed that vaccination with vaccinia virus recombinants NiV-G & F-proteins resulted in production of neutralising anti-bodies & prevention of lethal vaccinia virus infection in mice & hamsters (2006) Guillaume et al.

More current research on vaccination has continued to be built on G & F-proteins. The G-glycoprotein of HeV was used to create a subunit vaccine that looked to be effective in preventing infection with NiV in ferrets that had received lethal doses of NiV. HeV & NiV share 83% of same amino acid sequence. Despite the viral genome being found in two of the five ferrets, none of them displayed any symptoms of illness 2013 (Pallister et al.).

Additional vector-based immunisations are also under develop-ment. The ChAdOx1 NiV-B vaccine uses an an adenovirus vector in simian that encodes NiV-B glycol-protein G. Female Golden Syrian hamsters received a

range of doses of before receiving the NiV-B vaccine. some of which were followed by a booster dose after the vaccination. All of the animals had virus-neutralizing anti-bodies after a single vaccination, and all of the vaccinated animals lived through entire research without any viral RNA being found in oropharyngeal swabs & on necropsies. The virus has been found. However, oropharyngeal swabs and tissue collected after necropsy showed that control animals suffered wt. loss, respiratory, neuro-logical, and/or other symptoms 2019 (van Doremalen et al.).

Animals examined with NiV-M exhibited equal results; however, animals exposed to HIV had less favourable results.

Table.1: To stop the Nipah virus, vaccines are being developed

Vaccines	**Description**	**Animal Model**	**Reference**
Subunit-based			
(Equivac HeV) HeV-Sg	Using soluble HeV G glycoprotein as a basis, a subunit vaccination. elicits an immunological response that is cross-protective against HeV and NiV. available in Australia for horses	Ferret	(Pallister et al., 2013)
Vector-based			
NiVB ChAdOx1	NiV-B glycoprotein G recombinant simian adenovirus-based vaccination	Syrian hamster in gold	(van Doremalen et al., 2019)
rVSV-ΔG-NiVB/F-GFP	vaccination for the Vesicular Stomatitis Virus (VSV) that is recombinant and expresses NiV-B F or G	The challenge of the African green monkey	(Mire et al., 2019)
rRABV/NIV (NIPARAB)	Recombinant rabies virus vector expressing NiV G	C57BL/6 mice	(Keshwara et al., 2019)
Virus-like particle-based			
NiV-VLP vaccine	G, F & M-proteins from purified particles resembling Nipah	Syrian hamster challenge in gold	(Walpita et al., 2017)

	viruses		
m-RNA-based			
shelving m-RNA LNP	m-RNA vaccination that produces a soluble HeV glycol-protein component	Hamster from Syria	(Lo et al., 2020)

Nano-based Antiviral Treatment:

The type & form of NPs used have a signi-ficant impact on how adaptive viral inhibition is. To understand anti-viral activity of NPs, one must have a thorough grasp of the diverse NP types & nano-based systems. Examples of nano-based antiviral medications include hybrid nanosystems, simple inorganic NPs nano-systems & complex organic compounds. Metallic NPs (MNPs) in forms of nano-scales, nano-spheres & nano-capsules are included in the category of non-metallic NPs (INPs). A subset of organic NPs (ONPs), which are primarily characterised by their chemical composition, are nano-capsules in the form of NCs. Inorganic-organic, (nano-composites) & organic-organic components combine to form standardised hybrid nano-particulated systems, which are then applied to specific locations & tailored to meet specific needs (2013) Mandal et al.

Conclusion:

The Nipah virus, which has a high rate of epidemic fatalities, has been reported in a lot of impoverished countries. In the 20 years since the first case was reported, there hasn't been a substantial breakthrough in the range of treatments or a trustworthy vaccination. However, with the correct education, further outbreaks might be prevented. This should be the main priority in the fight against NiV epidemics. The fruit bat species Pteropus spp. appear to be natural reservoir hosts for NiV, however there is growing evidence that virus is quickly adapting to novel hosts and modes of transmission. The NiV virus was being transmitted from sick humans to pigs, horses, bats, & other animals just a few years after it was originally identified. Due to a single spillover event, a pathogen with the ability to transmit from person to person may only result in a few minor, localised outbreaks of infection, but repeated spillover events might result much greater disease burden. Physical barriers that prevent trans-mission of NiV from bats to humans may offer some pro-tection, but out-breaks continue to occur & risk of human-human trans-mission endures. More comprehensive public health measures, such as education, hygiene, and animal husbandry practises, as well as continued research into antiviral medicine treatments and immunisations, are necessary to prevent potentially larger future outbreaks.

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