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Review Article

Exposing Nipah virus: an epidemiological study of another thread in Kerala, South India

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ABSTRACT

Bats spread the Nipah virus, which causes severe encephalitis and high mortality. Multiple reports have come from Malaysia, Bangladesh, Singapore, and India. Pteropus fruit bats are known to host the virus. The virus has caused four outbreaks in Kerala in the past quinquennium. Scholars believe the virus is indigenous to the state's bat population. Climate change, resource depletion, deforestation, natural terrain changes, farming, and industrialization all contribute to viral disease outbreaks. In this review, we will discuss the epidemiological background of the previous NiV outbreak. We will also examine the transmission method epidemic prevention and control strategies and possible causes of the outbreak. Four Nipah epidemics have occurred in Kerala in the past five years. Expert investigation suggests that the virus may be endemic in the state's bat population. Kerala, India, has many bat species. In 2018, research found viral infections in the local fruit bat population. Traditionally, people eat fresh toddy or sap from trees, which can be polluted by bats carrying the Nipah virus. Kerala's healthcare system also closely monitors unexplained fevers for Nipah virus infections. The World Health Organisation and Indian Council of Medical Research found that the entire state is susceptible to Nipah virus infections. The virus is a major cause of encephalitis outbreaks, which have high mortality rates, mostly in Indo-Bangladesh.

Keywords: Nipah virus, NiV, Kerala, Fruit bats, Palm sap, Pig, Zoonotic virus, Threat, ICMR, WHO, Mortality, India, Bangladesh, Bats, Viral infections, Encephalitis, Endemic

INTRODUCTION

NiV, or Nipah virus, is a member of the family *Paramyxoviridae*, genus *Henipavirus*. It is an enveloped pleomorphic virus. The viral genome is roughly 18.2 kilobases in length, and it is a non-segmented negative-sense single-stranded RNA. All six of the viral structural proteins-the nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G), and RNA polymerase (L) are encoded by this single RNA sequence. The N, P, and L proteins, coupled with the viral RNA, form the ribonucleoprotein complex (Figure 1), which is essential for transcription regulation and viral RNA synthesis.[1] The F and G proteins are transmembrane proteins found inside the viral envelope that control attachment and entrance into the host cell. It is the G protein's job to help the virus connect to host cells. It does this by connecting with a set of cellular receptors called Ephrin-B2 and Ephrin-B3.[2] However, the F protein is essential in starting the process of membrane fusion between the virus and the host cell. The virion enters the host cell via this fusion process.[3]

Hendra virus (HeV) and Cedar virus, both belonging to the genus *Henipavirus*, are two additional species that have been acknowledged in scientific literature. The numerical value provided by the user is insufficient to

generate a response in the format of a research student. According to our findings, it has been observed that subjecting the virus to a temperature of 60 °C for 60 minutes leads to its inactivation. The observed phenomenon exhibits stability within the pH range of 4.0 to 10.0. The organism in question demonstrates remarkable resilience, exhibiting prolonged viability under optimal circumstances. Specifically, it has been observed to persist for extended durations, ranging from several days, within the medium of fruit bat urine, to comparable timeframes within fruit juice that has been compromised by contamination. The susceptibility of the subject under investigation to commonly used soaps and disinfectants has been observed. In the context of outbreaks, the utilization of lipid solvents, such as alcohol and ether, as well as sodium hypochlorite solutions, has proven to be efficacious for disinfection purposes.[5]

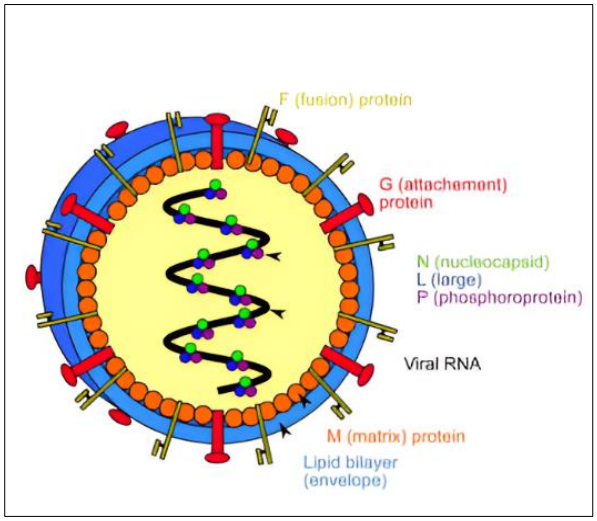

Figure 1: Nipah virus.[4]

Mechanism

The infection of endothelial cells has been recognized as a significant focal point; yet, the mechanism by which the virus disseminates to the central nervous system remains unidentified.[6]

Transmission

Fruit bats have been identified as the primary natural reservoirs of the disease in question. During the initial outbreaks in Malaysia and Singapore, it was observed that the majority of human infections were primarily attributed to direct contact with afflicted pigs or their contaminated tissues.[7] In the context of the Malaysian outbreak, it is noteworthy that the transmission of the virus initially occurred from its natural host, namely fruit bats, to an amplification host, namely pigs, before ultimately infecting humans. However, it is worth mentioning that in subsequent outbreaks, the need for an amplification host was absent. The outbreaks in Bangladesh and India were attributed to the consumption of fresh date palm sap that had been contaminated with NiV, which was found to be present in the urine or saliva of fruit bats.[8] Additionally, it is worth noting that there were instances of person-to-person transmission, particularly within a hospital setting in India. It is intriguing to observe that approximately 75% of the reported cases were attributed to hospital staff or visitors. NiV cases exhibit a propensity for clustering, often manifesting as outbreaks.

However, it is worth noting that a notable proportion, specifically 18%, of the reported cases in Bangladesh were observed as isolated occurrences. The initial statement provided by the user lacks sufficient context or content to be rewritten in a research student-like manner The potential susceptibility of dogs and cats to Nipah virus has been documented in previous studies. However, the viral infectivity in chickens remains to be elucidated, as limited research has been conducted in this specific area.[9]

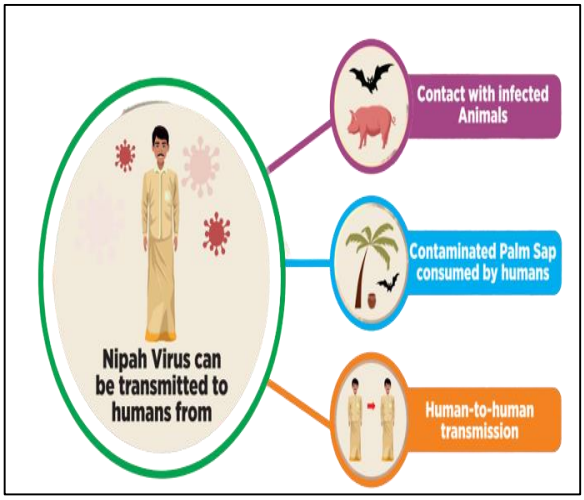

Figure 2: Transmission of NiV.[12]

Consequently, the current understanding regarding NiV infection in chickens is inconclusive and necessitates further investigation to ascertain their potential susceptibility to this pathogen.[10] Despite conducting a thorough search, the source of the latest outbreak in Kerala has yet to be identified. According to extensive wildlife studies, it has been observed that the virus has exhibited a wide distribution pattern across a significant portion of Asia and Africa, affecting no less than 10 genera and 23 distinct species of bats.[11]

Pathogenesis

Steps involved in Pathogenesis of NiV

NiV has been found in bronchiole epithelial cells early in infection.

The research suggests that NiV antigen can be found in the bronchi and alveoli.

Airway epithelial infection activates inflammatory mediators.

In advanced disease, the virus infects pulmonary endothelial cells.

According to research, viruses can enter the bloodstream and spread throughout the body. This dissemination might occur freely or through binding to host leukocytes.

This procedure allows the virus to enter the brain, spleen, and kidneys.

Two pathways: hematogenous and anterograde via olfactory nerves, allow viruses to enter the CNS.

After virus infection of the central nervous system (CNS), blood-brain barrier (BBB) breakdown and IL-1b and TNF-a expression cause neurological symptoms. Red text indicates human symptoms.[14]

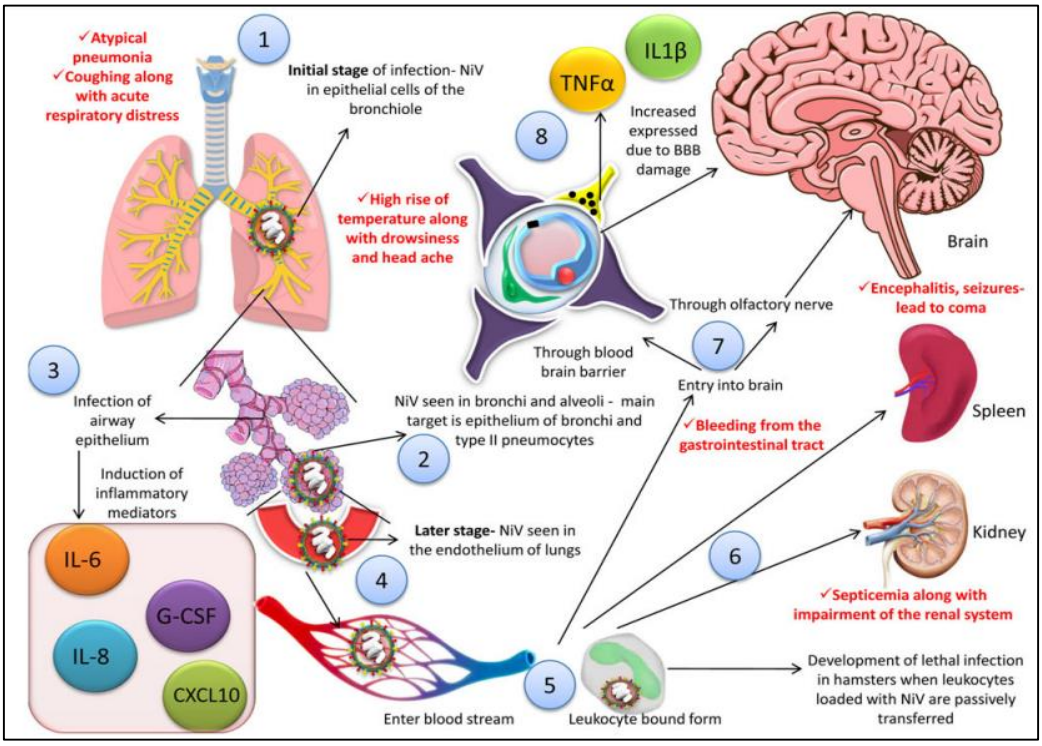

Figure 3: Pathogenesis of NiV.[13]

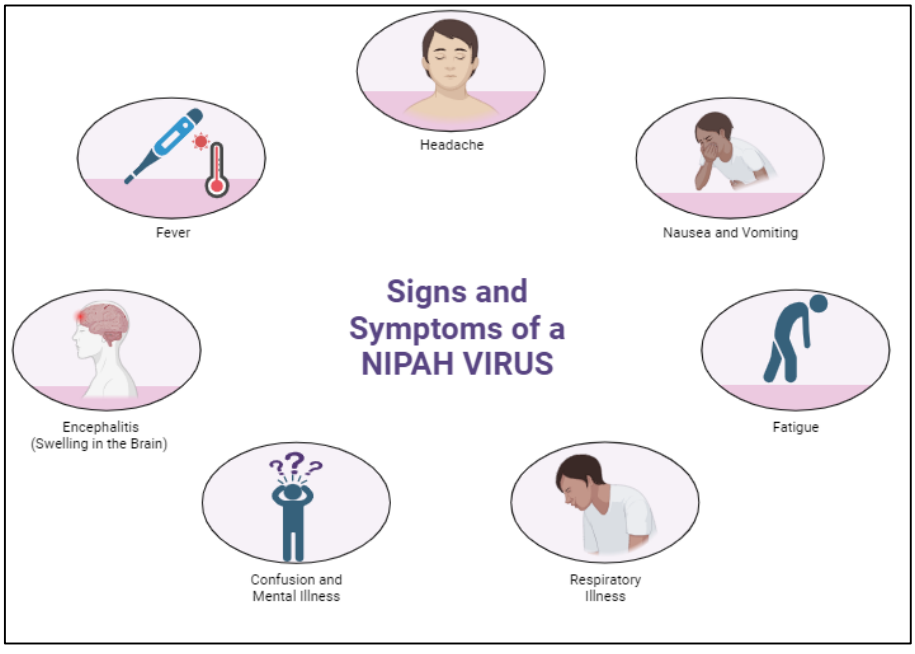

Figure 4: Symptoms of NiV.[15-17]

Clinical features

The median disease incubation duration was 9 days, ranging from 4 to 21 days. The most prevalent symptoms were fever, headache, cognitive impairment, extreme asthenia, coughing, respiratory distress, emesis, and convulsions

Historical outbreaks and their geographic distribution

The table below shows where *Pteropus* species, which are also called "flying foxes," are found around the world and how they are related to the virus family *Henipavirus*. Patients who were affected by the NiV in Bangladesh, Malaysia, and Singapore were able to give samples of the virus that were isolated from their bodies. The *Hendra* virus, which is a disease that can spread from animals to people, was found in Australia. As the asterisks in the data show, bat virus isolates have been successfully taken from *Pteropus hypomelanus* in Malaysia, *Pteropus lyeli* in Cambodia, and *Pteropus police phallus* in Australia. Most of the proof we have about bat infections comes from finding antibodies that only react with Hendra virus, Nipah virus, or an unidentified cross-reacting *Henipavirus*.[18]

Table 1: Evidence and confirmed human *Henipavirus* infected countries.[19]

Evidence for *Henipavirus* in bats	Confirmed human *Henipavirus* infection
Australia	Malaysia
Malaysia	Singapore
Singapore	Bangladesh
Bangladesh	India
India	-
Some other India Ocean countries	-

Table 2: NiV outbreak in Malaysia.

First Case Reported	1998-1999
Reported at	Village of Sungai Nipah
States or district	Perak, Selangor, Negeri Sembilan states
Death	105
Mortality rate	40%
Total cases	265

Table 3: NiV outbreak in Singapore.

First case reported	1999
Reported at	Singapore
States or district	Singapore
Death	1
Mortality rate	10%
Total cases	11

Table 4: NiV outbreak in India.

Reported (in year)	District (state)	Transmitted by	Cases	Death	Mortality rate (%)
2001	Siliguri (West Bangal)	Direct Contact between humans, contact with bats	66	45	68.2
2007	Nadia (West Bengal)	Unknown	5	5	100
2018	Kozhikode, Malapp-uram districts, (Kerala)	Unknown	19	17	89.4
2021	Pazhur, Kozhi-kode (Kerala)	Unknown	1	1	100
2023*	Kozhi-kode (Kerala)	Unknown	6	2	33.33

* Outbreak is ongoing.

Previous research on Nipah virus, including studies on transmission and treatment

Vaccine platforms for NiV

It has been found that the recombinant measles virus (rMV) vaccine that expresses the envelope glycoprotein of NiV is a good option for a vaccine.

In the past few years, a hybrid vaccine based on the vesicular stomatitis virus (which can reproduce) and encoding a glycoprotein of NiV has been made.

Nipah virus-like particles (NiV-VLPs) made up of three NiV proteins G, F, and M from mammalian cells have been made and tested as a vaccine in BALB/c mice.

T-cell epitopes of NiV infectious proteins were predicted and modeled using immunoinformatics to help make a peptide-based vaccine against NiV.[21]

Outbreak in Kerala

Timeline of the Nipah Virus outbreak in Kerala

First Outbreak in 2018

NiV encephalitis was confirmed in 18 patients and one main case in Kozhikode, Kerala, in May 2018. Rare occurrence. As in Bangladesh and Siliguri, the disease

spread from person to person. The outbreak NiV was 97% the same as the Bangladeshi NiV. There were fewer cases than in the Siliguri (66 cases) and Bangladesh (44 cases) outbreaks, but more than in random outbreaks in Bangladesh (3-16 cases) and Nadia (5 cases). As in Siliguri and Bangladesh, the seasonality matches South India's January-May fruit-bearing season. This is also *Pteropus* bat breeding season. The CFR (88.8%) is slightly higher than Siliguri (68%) and Bangladesh (77%). The lower Malaysian epidemic death rate (40%) is attributed to the distinct NiV. The sickness propagated from person to person, and case 0 caused 15 verified cases. Once sick, everyone acquired it from health care. While case 0 was at hospital B, his family may have fallen sick. Hospital patients in Siliguri infected 33 healthcare professionals and visitors, spreading the virus for the first time. They were also seen in Bangladesh. Local bats were mapped, and 19% of *P. giganteus* samples had NiV. Found no other animal hosts. Drinking raw date palm sap is rare in Kerala, however the initial instance may have been exposed to bats from the well or forest. Pigs are not expected to be intermediate hosts in this epidemic because there are no pig farms nearby. The NiV sequences in *P. giganteus* and human NiV samples from Kerala match 99.7% to 100%, according to phylogenetic analysis at NIV, Pune. The youngest sick person was 19, but all the others were adults. Men more than women became sick. Men over 15 were 1.4 times more likely to be infected during the Siliguri pandemic. Bangladeshi youngsters as young as 2 and as old as 60 have contracted the disease. The Kozhikode outbreak did not affect children. This may have been because children had little contact with sick people during the infectious phase. The disease spreads from hospitalized patients. As demonstrated in Siliguri, most disease spreads in the late stages, when symptoms like encephalitis and problems breathing are severe and droplets and contact secretions are very contagious. Bangladesh (9 days) and Malaysia (10 days) outbreaks started spreading at the same rate. Only two health professionals became sick and one died. Both were exposed before the outbreak, unlike the Siliguri outbreak, which sickened more healthcare personnel. No more people got sick after the virus was detected and isolated. Increased barrier breastfeeding prevented the spread.

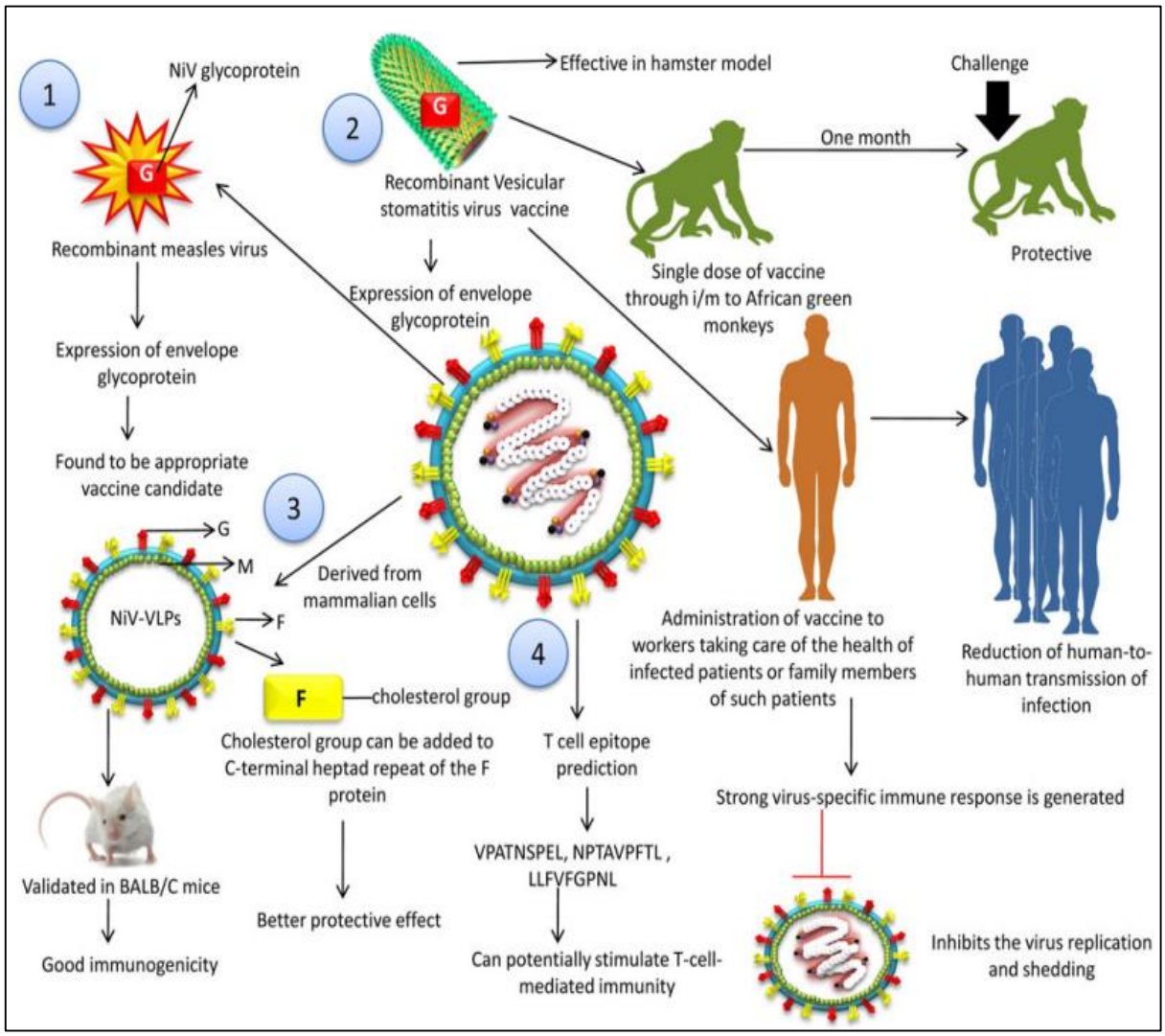

Figure 5: Vaccine development for NiV.[22-25]

Incident cum outbreak in 2019

A 23-year-old Kochi student was a new case on June 4, 2019. Although over 300 people were monitored, no new instances were found. The child recovered. India has experienced this four times. There were 45 deaths in 2001, 5 in 2007, and 17 in 2018.

Second outbreak in 2021

One case of Nipah virus was identified in Kozhikode, India, on September 4, 2021. Kerala State Health Department reported this. Nipah, a novel zoonotic disease with a high death rate, is relevant for public health in South East Asia and the Western Pacific WHO Regions. India has had the sickness five times.

His family took a 12-year-old boy with a low-grade fever to a neighboring hospital on August 29. As his condition declined on August 31, he was transferred to different hospitals. On September 1, the patient's family requested a transfer to a Kozhikode hospital as his health declined.

The National Institute of Virology in Pune, India, collected plasma, blood, and cerebrospinal fluid on September 3. On September 4, plasma, cerebrospinal fluid, and serum samples were tested for the Nipah virus using RT-PCR. Plasma samples were tested for IgM antibodies using ELISA serology. September 5 saw the patient's burial and burning in Kozhikode.

As of September 6, epidemiological studies discovered quarantined healthcare workers and immediate family members.[26]

Third outbreak in 2023

The Nipah virus has killed people in the southern Indian state of Kerala for the fourth time since 2018. Two deaths caused by the virus informed the government to the outbreak. Mohammed Ali, who lived in the village of Maruthonkara and was 49 years old, died on August 30, and Mangalatt Haris, who lived in the town of Ayanchery and was 40 years old, died on September 11.

On September 13, test results showed that both guys had died from Nipah. Routine nose tests were used to check for the virus. A mix of flu-like and neurological symptoms, like a headache, fever, cough, shortness of breath, and seizures, made them think they should test for the virus.

The virus was first found in pig farmers in Malaysia in 1999. It is possible that infected pigs spread it to people at that time. Dr. Thekkumkar Surendran Anish, an associate professor of community medicine at the Government Medical College in Manjari, Kerala, who is in charge of the state's monitoring team and spoke to NPR about the situation, says that there was no human-to-human transmission during the Malaysian outbreaks.[9]

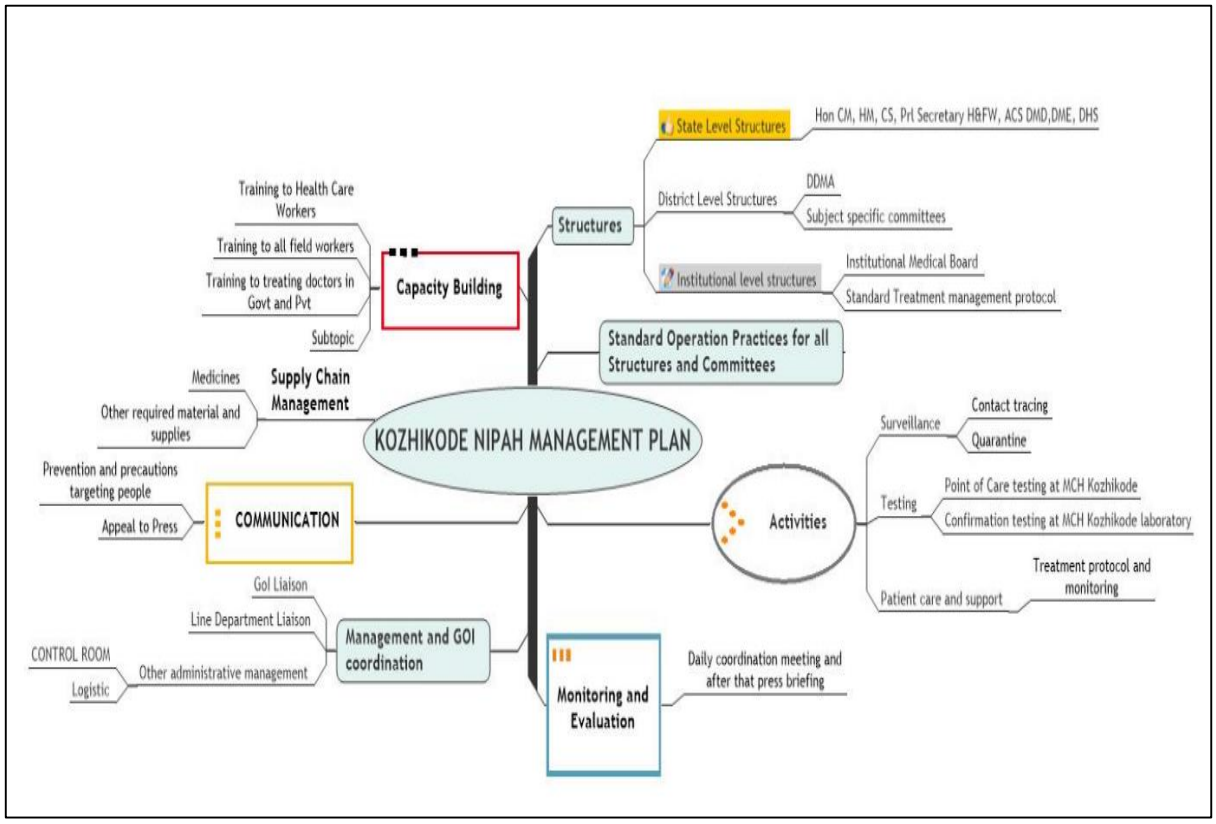

Figure 6: Management plan by Health and Family Welfare Department, Government of Kerala.[21]

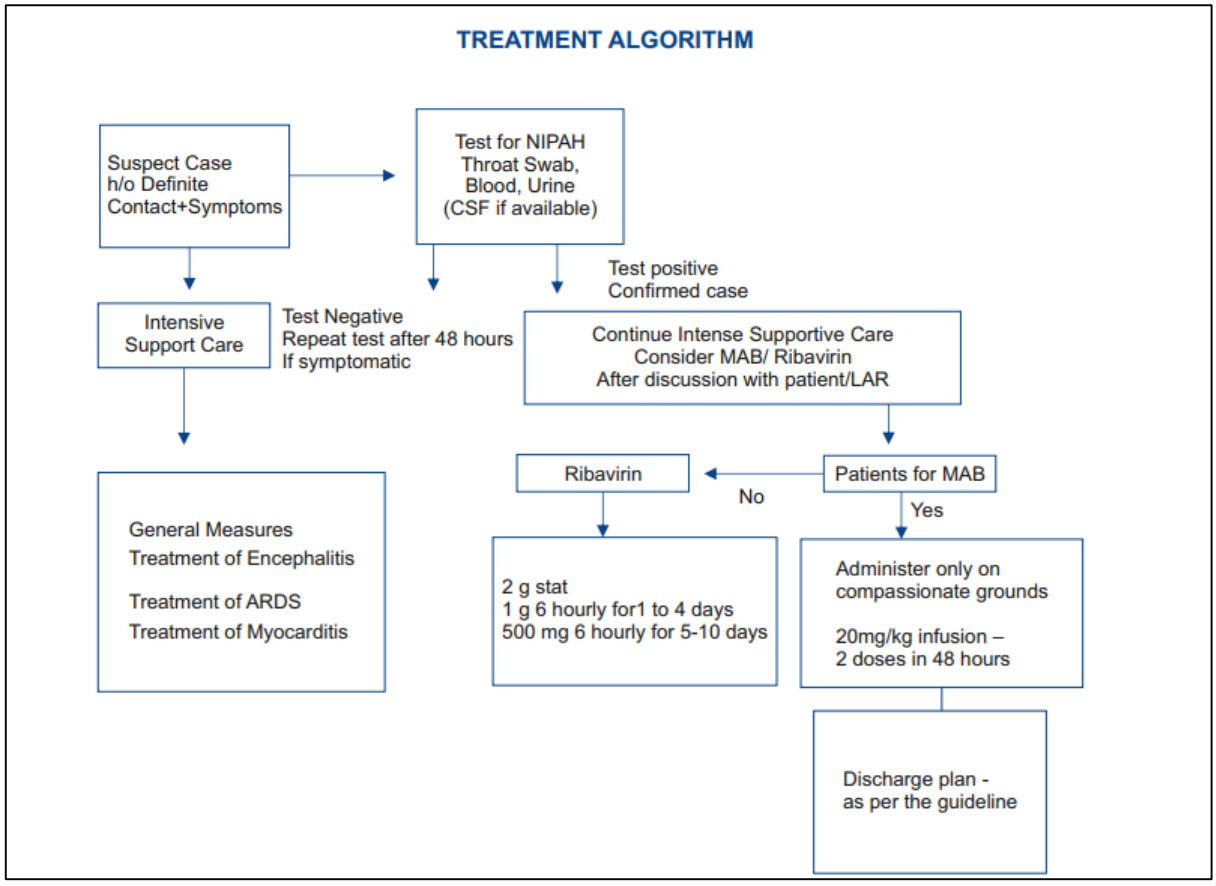

Figure 7: Treatment Logarithm by Government of Kerala.

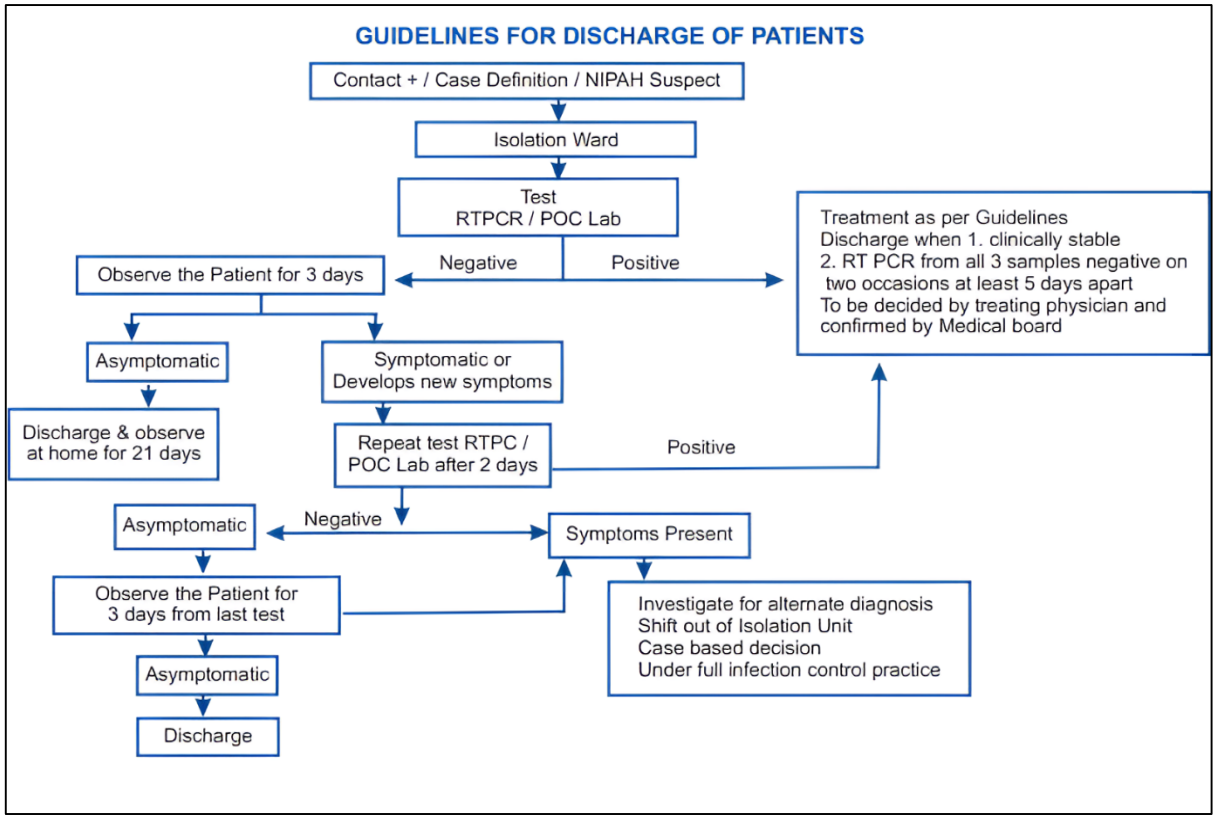

Figure 8: Discharge of patient's guideline, Launched by Government of Kerala, India.

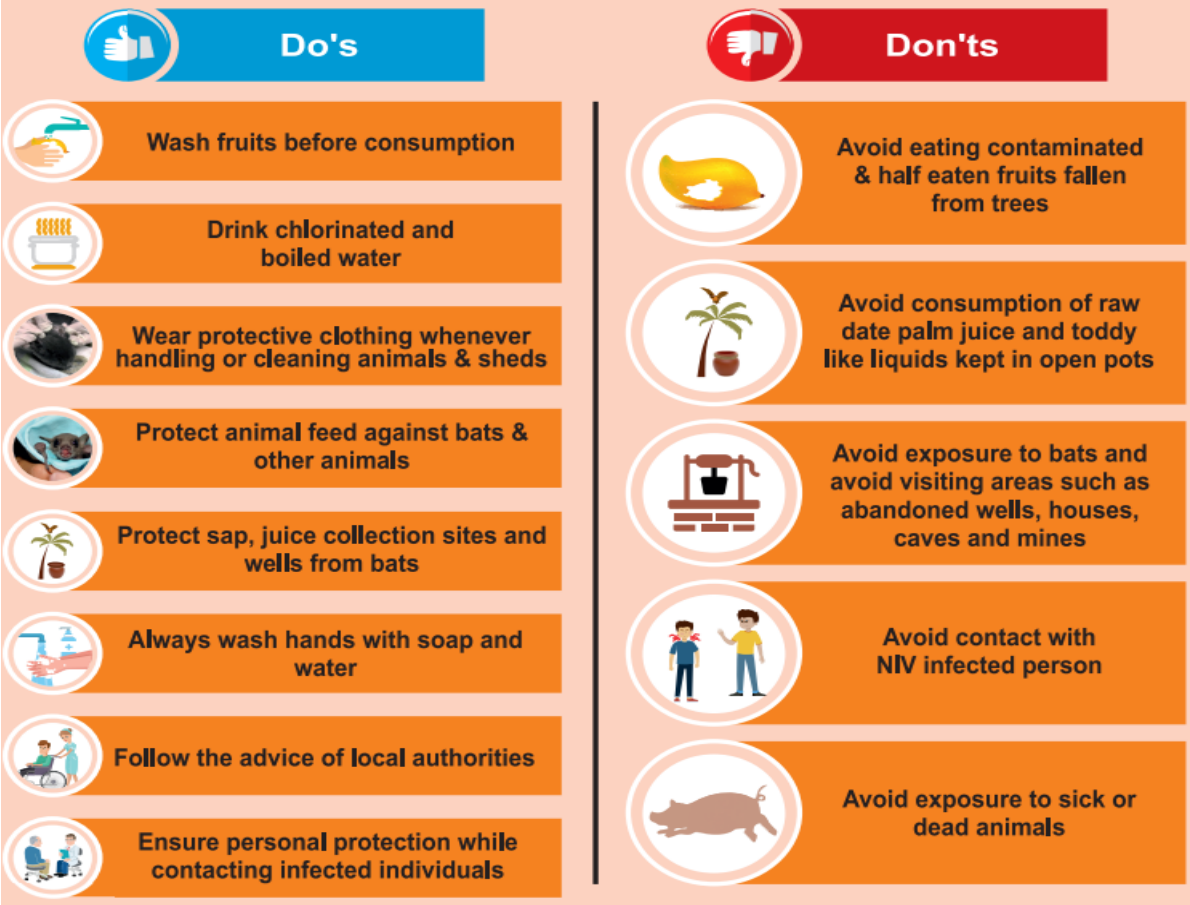

Figure 9: DO's and don'ts in NiV.

Epidemiological data on the affected individuals and areas

The NiV has caused concern and research in Kerala for years. Zoonotic viruses like NiV can spread from animals to humans. This usually occurs when people eat contaminated foods or touch diseased animals, especially bats and pigs. Here's a public health overview of NiV spread in Kerala.

Breakouts and incidence: Kerala has had many NiV outbreaks since 2018. These epidemics have occurred intermittently and varied in severity. The high fatality rate of NiV in Kerala has garnered notice despite its low case rate.

Geographical spread: These cases have mostly occurred in Kozhikode and Malappuram, Kerala. Some settlements have had multiple outbreaks. Their global expansion emphasizes the need to monitor and regulate high-risk locations.

Transmission dynamics: In Kerala, the NiV spreads by intimate contact with carriers. This includes family members and health care providers who have treated Nipah patients. Community members have contracted the sickness via infected body fluids.

Reservoir host: Fruit bats (*Pteropus* spp.) may be NiV's reservoir hosts. Bat excrement and partially eaten apples can make people sick. Future outbreaks can be prevented by understanding bat-human communication.

Kerala's public health agency has tracked down and isolated NiV carriers and held public awareness campaigns. Work has also improved hospital infection control and healthcare worker safety.

Research, monitoring: The virus, how it spreads, and what could cause it to spread are being studied and monitored in Kerala. Local and foreign scientists have collaborated on NiV studies to educate locals.[28]

Control measures in Kerala

Response and control measures implemented by the government and health authorities, Management plan by Health and family welfare department, Government of Kerala was introduced.

Treatment logarithm by H&FW, Government of Kerala is shown in Figure 7.

Diagnosis, differential diagnosis, treatment, discharge, and prevention measures

Throat and nasal swabs, CSF, urine, and blood should be utilized to identify the virus and undertake real-time polymerase chain reactions early in sickness. ELISA (IgG and IgM) can detect antibodies in the future.[9] Most people's CSF has normal glucose and high protein. A person with encephalitis who has a normal WBC count and CSF chemical components may nonetheless have NiV.[8] Isolating and growing NiV requires BSL-4 facilities. Primary viral isolation from suspected samples can be done under BSL3 conditions with strong operator protection restrictions. In Pune, India, the National Institute of Virology (ICMR) opened a BSL4 lab. This lab has everything to diagnose NiV and is ready for anything in the country. Other viral encephalitis kinds include Japanese, Rabies, and *Herpes Simplex*. NiV treatment is currently unavailable to humans and animals. Mixed effects have been seen with ribavirin, an antiviral. In a ferret model, m102.4, a neutralising human monoclonal antibody that identifies the NiV G glycoprotein receptor binding region, showed potential.[29]

Prevention

If there is a chance of a spread of Nipah, the places where animals live should be put in quarantine. When taking care of sick people or sick animals, you should be careful. Samples from people and animals thought to have Nipah should be taken by trained staff taking the usual safety measures.[21,30]

CONCLUSION

In conclusion, the emergence of NiV in Kerala illustrates the importance of rigorous monitoring, effective public health response, and continued research to limit zoonotic disease risks. Kerala's experience with the NiV can teach the world health community how to handle future viral infections that harm humans and animals.

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