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Review Article

Unraveling Nipah Virus: Key Insights on Spread, Symptoms, Management

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Abstract

According to the World Health Organization (WHO), a newly identified zoonosis that poses a major risk to both humans and animals is the Nipah Virus (NiV). The infectious agent known as NiV is responsible for devastating illnesses in both people and animals. It was initially found in the *Pteropus* genus fruit bats and the *Pteropodidae* family. The most frequently identified route for transmitting NiV is ingesting fresh date palm sap, among other possible mechanisms. Another potential route for NiV to spread from bats to humans through domestic animals. The NiV mostly affects respiratory and neurological tissues, resulting in neurological symptoms and respiratory difficulties in those who are off. The immune system's ability to fight the virus is crucial, and this includes interferon-mediated pathways and innate immunological responses. NiV is regarded as a BSL-4 disease since there is no known cure or vaccine to prevent it only personal care including symptomatic treatment, hydration management, and breathing help, remains the mainstay of care. Three pharmaceutical options for the possible treatment and post-exposure prophylaxis of NiV infection have been studied: ribavirin, favipiravir, and m102.4 monoclonal antibody. This review will give an overview of the virus, explain the circumstances behind its emergence, and speculate on when it might spread to other parts of the world.

Keywords: NiV- Nipah Virus; World Health Organization; pathogenesis, vaccines

INTRODUCTION

The World Health Organization (WHO) states that NiV is a recently discovered zoonosis that can seriously harm both humans and animals. Nipah is an infectious agent that causes serious infections in both humans and animals.[1] In other words, aside from the virus's natural hosts, it was first discovered in fruit bats belonging to the *Pteropodidae* family, *Pteropus* genus. Globally, emerging infectious diseases pose a serious threat to public health.[2] Roughly 75% of the diseases that are thought to be emerging are zoonotic, or able to spread naturally between humans and animals. The NiV is a zoonotic virus that infects humans and other animals and is carried by bats (fig. 1).[3]

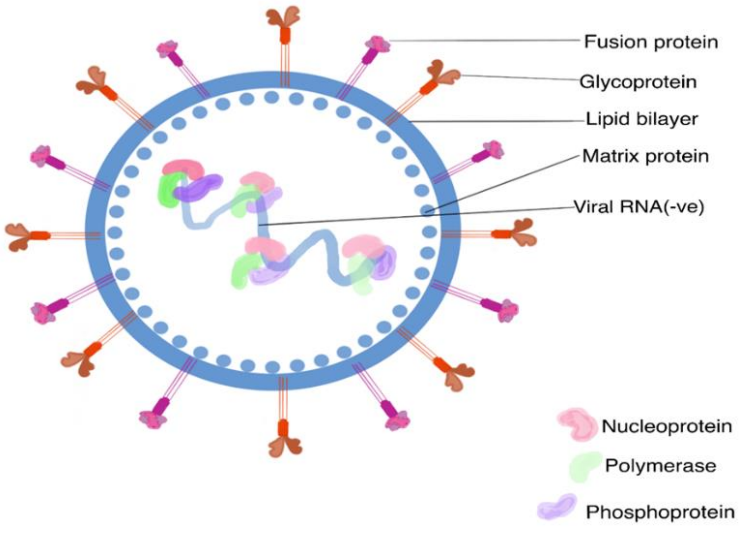

Figure 1: Structure of Nipah Virus.[4]

Human-killing viruses such as the NiV, SARS-CoV, Ebola virus, Marburg virus, and rabies virus can be transmitted by bats. [5] NiV can also spread from bats to people directly, without the need for a middle host. The NiV is a virus that causes encephalitis and gives rise to the novel genus *Henipa virus* within the *Paramyxoviridae* subfamily. These viruses have non-segmented, negative-stranded RNA genomes. Examples of these viruses are the measles, mumps, and Hendra virus. [6,7] The zoonotic virus known as NiV first appeared in Peninsular Malaysia's Negeri Sembilan state in the Port Dickson area of Bukit Pelandok in 1998. It resulted in a significant respiratory disease outbreak in pigs and severe encephalitis in those who died at a rate of about 40%.[8] A total of 265 Nipah encephalitis patients were confirmed during these outbreaks in Malaysia; of them, 105 (or 39.6%) deaths were reported.[9] Date palm sap consumption and person-to-person transmission caused the initial outbreak in Bangladesh, which occurred in April 2001 and affected the northwest and central parts of the nation.[10] Three paths of NiV transmission from bats to humans have been discovered by epidemiological investigations conducted in Bangladesh. Ingestion of fresh date palm sap is the pathway most often implicated. Domestic animals are a second way that NiV might spread from bats to humans in Bangladesh. Third, direct contact with bat secretions contaminated with NiV may occur for certain individuals. Studies using infrared cameras verify that P. giganteus bats often visit date palm sap plants and sip the sap when gathering it.[11] Up until 2015, 13 Nipah yearly outbreaks were reported from different regions of Bangladesh; 261 laboratory-confirmed cases and 199 (76.2%) deaths were the outcomes.[7] An outbreak of infectious febrile diseases took place in and around the northern West Bengal city of Siliguri at the beginning of 2001. The second NiV outbreak was discovered in April 2007 in the West Bengali region of Nadia, close to the Bangladeshi border in the village of Belechuapara. The case fatality rate for this outbreak was 100% since every infected person passed away within a week of infection, even though it only affected five people. On May 19, 2018, reports of the third and most current epidemic came from the southern Indian state of Kerala, in the Kozhikode region.[11]

In the National High-Security Animal Diseases Laboratory in Bhopal, samples of Pteropus bats were gathered from the Kozhikode district and examined. After 52 samples were obtained, 10 (19.2%) of them tested positive for NiV using RT-PCR.[7] All three of these 89 laboratory-confirmed cases, including 67 (75.2%) fatalities, were linked to NiV outbreaks. In humans, the virus can take two weeks to two months to incubate.[6] High temperature, headache, nausea, vomiting, aberrant eye reflexes, vasomotor abnormalities, seizures, and myoclonic jerks—all of which are indicative of brainstem dysfunctions—are common symptoms of severe NiV encephalitis.[12] The United States Food and Drug Administration (FDA) implemented the Animal Efficacy Rule in 2002. When human efficacy studies are impractical or unethical, this rule particularly applies to the development of medical countermeasures. This guideline essentially permits the assessment of treatments or vaccinations using information obtained from studies conducted in two animal models.[13] In this review, we have outlined the histology, clinical features, and history of NiV encephalitis. We go over data regarding the pathogen's epidemiology in its natural habitat as well as current theories regarding the factors that may have contributed to its establishment in Bangladesh and Malaysia. Lastly, we talk about the possibility that Nipah and kindred viruses would eventually spread to Australia, Asia, and other regions.

EPIDEMIOLOGY

Dr. Kaw Bing Chua discovered and identified the first NiV in 1999 following an outbreak of encephalitis in a group of hog farmers and merchants in Malaysia and Singapore that led to the fall down of the billions of dollars' worth of exporting of the pigs.[4] The pandemic was named after the village of Kampong Sungai Nipah where the disease was first discovered.[14] Pteropus fruit bats have been recognized as the natural reservoir of NiV. This illness may affect humans and animals, including pigs, equally.[3] It can spread from person to person and from animal to person from pigs and bats already suffering from NiV. The only strategy to treat extremely deadly, infectious illness is to give quick care according to symptoms. The outlay of NiV infection case fatalities was quite elevated.[15] Therefore, it is essential to understand the epidemiological characteristics of NiV illness to design future interventions, controls, and preventions. The countries that are affected by the Nipah virus, or exaggerated outbreaks of the Nipah virus are Malaysia/Singapore, Bangladesh, and India.

MALAYSIA/SINGAPORE

In many Malaysian pig farming communities, there was a viral encephalitis outbreak from September 1998 to June 1999. Subsequently, Singaporean abattoir workers were affected by the pandemic. Nearly 100 individuals were hospitalized at the University Hospital in Kuala Lumpur, while over 200 patients were afflicted statewide. It was determined that a novel paramyxovirus that is closely linked to the Hendra virus was the source of the epidemic.[16]

The research had 110 individuals in all, from 14 families. Thirty-seven household members denied the Hendra serology test and the interview. They were all clinically asymptomatic, albeit the other household members could provide their clinical histories.[17] The 73 members of the family who gave their agreement for the interview and serology had an average age of 34 years. The male-to-female sex ratio was 2.5 to 1, and the ethnic composition was Indian and Chinese. Thirty people (or twenty-seven percent) in the home had a symptomatic Nipah infection. Six (8%) of the forty-three clinically healthy participants who underwent serology testing were positive, suggesting a prior subclinical infection.[18] As a result, 35% of the entire family was infected with the Nipah virus, and most of them were symptomatic. The 73 members of the family who gave their agreement for the interview and serology had an average age of 34.7 years (14 to 64 years).[3] The ratio of male to female sex was 2.5 to 1. The ethnic makeup was Indians and Chinese (81

percent each) (19 percent). Thirty people (or twenty-seven percent) in the home had a symptomatic Nipah infection. Six (8%) of the forty-three clinically healthy participants who underwent serology testing were positive, suggesting a prior subclinical infection.[19] As a result, 35% of the household members overall had a Nipah infection, with the majority exhibiting symptoms. There was an average of 7.9 families per household. Before and during the epidemic, seven out of fourteen families (about fifty percent) reported that their pigs had strange illnesses. The digit for suffering patients from the houses with hogs having symptoms of NiV did not differ statistically from the number of households reporting no signs of sick pigs.[20,14]

Pig farming settlements in Ulu Piah were originally affected by the Nipah encephalitis epidemic. Around Ipoh, which is 200 kilometers (about 124.27 mi) north of Kuala Lumpur, are Tambun and Ampang. Following that, the outbreak spread to the pig farming communities in Sepang and Sungei Buloh in Selangor, Tanah Merah in the State of Negri Sembilan, Bukit Pelanduk (containing Sungei Nipah and Kampong Sawah), and Sikamat. Bukit Pelanduk was home to the majority of the sick. Around ten thousand people are living in Bukit Pelanduk, a collection of pig farming settlements.[12] There were 79 Malay people, and the remainder were Indians and ethnic Chinese. The village's primary source of income was pig farming and the accompanying support industries. According to this study, the NiV generated a peak infection rate that affected 33% of members of households living on contaminated farmland, with 27% of them exhibiting symptoms. Those who worked as farmers full-time had a greater risk of symptomatic infection at 51 percent.[7] This is consistent with a peak rate of 56% of household infections among hospitalized patients. In the affected farms, 8% of the household members experienced subclinical illness as a result of the infection. The case-control study by Parashar et al. calculated that the asymptomatic seropositive rate was 11%.[21] In Singapore, two toilet workers had positive asymptomatic Nipah serology and 11 of them were diagnosed with clinical disease. When compared to subclinical illness, the greater likelihood of symptomatic infection is unlike Japanese encephalitis, where only one out of Encephalitis was symptomatic in 300 affected patients.[18] A distinct encephalitis associated with pig rearing called Japanese encephalitis served as the primary differential diagnosis during the first epidemic. This study showed a link between the development of Nipah infection and full-time farming with significant pig exposure.[22] In Malaysia, the total reported cases during 1998-1999 were 265 out of which 105 were reported dead with a fatality rate of 39.6%.[23]

BANGLADESH

According to observational and epidemiological studies, all Nipah cases observed in Bangladesh from 2001 to 2010 were reported between December and May in the northwestern and central parts of the country.[24] The mortality rate of NiV infection in Bangladesh is over 70%. Recent research has identified the consumption of date sap, a popular food in Bangladesh, as the primary means of transmission of NiV to humans from bats.[25] The extraction of unprocessed sap from date palms happens in the winter seasons. During the winter months, coinciding with the duration when the majority of NiV cases were detected in Bangladesh. Consequently, this timeframe is commonly known as the 'Nipah season'.[26,27] Studies using infrared cameras show that fruit bats of the genus Pteropus, the main host of NiV, come to trees of palm at midnight. They infect the sap by licking the sap stem and urinating on the sap collection pot. Another prevalent route of NiV transmission in humans is by contact with infected individuals primarily through exposure to their respiratory secretions.[28] In Bangladesh, most person-to-person transmission occurs through family caregivers who provide care to Nipah patients at home and in hospitals. Additionally, the nosocomial spread of NiV to healthcare professionals has been accounted for in both Bangladesh and India. Postmortem human transmission of NiV was also reported during the NiV outbreak in March 2010.[29] Until 2006, the collaboration between the Ministry of Health and Family Welfare's Institute of Epidemiology of Bangladesh, Disease Control and Research (IEDCR), and the International Centre for Diarrheal Diseases Research (ICDDR) has entailed joint efforts in conducting hospital-based monitoring to track reports of NiV infection.[29] From December 2010 to March 2011, qualitative researchers and an epidemiologist joint team from IEDCR and ICDDR inquire into various groups and individual reports of NiV infection in Bangladesh. They aimed to detail NiV cases concerning time, location, and individuals, and to discern transmission risk factors. NiV patients were diagnosed during the 2010-2011 Nipah season.[30,31]

INDIA

The first outbreak in India occurred between the last weeks of January and the last weeks of February in 2001 in the Siliguri district, a major commercial city in the state of West Bengal. Samples from patients were laboratory tested retrospectively for NiV infection because Siliguri borders Bangladesh and initial laboratory tests did not identify the pathogen. [32,33] Serum samples from 9 out of the 18 patients reported positive for antibodies to NiV-specific immunoglobulin G (IgG) and immunoglobulin M(IgM), and upon urinalysis 5 samples were detected with NiV, RNA. This significant epidemic resulted in the death of 45 out of 66 confirmed cases, with a death rate of 68%. Not any kind of information about the actual index patient was available.[19] Nosocomial infections were the main reason for the transmission of NiV and no kind of transmission from animals was reported. The 2nd NiV outbreak was outlined in 2007 in Nadia (West Bengal), in this outbreak the 5 patients who were reported positive died within 10 days demonstrating a mortality rate of 100%.[34] The 3rd and most recent and most rigorous NiV outbreak was reported in Kerala in May 2018, where 23 patients were identified and reported positive for NiV, and the mortality rate was followed by 91%. On 2 May 2018, the outbreak was taken up when a 27-year-old man in Kozhikode was hospitalized with fever and muscle pain. He developed a high fever, vomiting, and paresthesia and was

transferred to another hospital, but he died. No blood samples were taken for NiV testing. Only nosocomial spread has been reported.[35] 22 cases of NiV infection were reported from index patients. Two patients have been survived the 23 infected patients, whereas 21 died, resulting in the highest mortality rate of 91%.[34,36]

On 30 May 2018, the epidemic was declared contained. Out of the 18 specimens collected, they all were reported positive for RNA of NiV, 13 patients were found positive for NiV-specific IgM antibodies, and 4 patients were reported positive for IgG antibodies. The only real sick and infected person in the entire city is a pet lover. Because the onset coincided with the bat breeding season, he is believed to have transmission of the virus from the infected pup. The main source of infection in Kerala is nosocomial infection.[37] Looking at the total number of cases in India, outbreaks in West Bengal accounted for 70% and 5% of all cases in India in 2001 and 2007, respectively, while Kerala accounted for approximately 25% of all cases in India. In both states, the epidemic has increased the number of deaths. A ditto case of NiV in 2019 was reported when a victim from Kerala's Ernakulam district reported positive for NiV. The Government of Kerala with a forward-thinking approach helped control the 2019 outbreak.[34]

About 300 people who were close to infected patients were monitored precisely for possible symptoms of NiV. The main patient was transferred for a high-security quarantine provision and is kept under surveillance, and contacts were advised to stay at home and immediately report any symptoms. Monoclonal antibodies to treat NiV were imported from Australia as a precautionary measure to prevent the possibility of sporadic outbreaks.[38] In addition, testing bases were established at local medical institutions, contributing to quick and accurate diagnosis. The recovery of index cases and suppression of the virus brought enormous praise to the healthcare sector and government planning to contain NiV in the year 2019.[39]

On September 12 to 15, 2023, the Ministry of Health and Family Welfare, Government of India, reported 6 positive cases of NiV, followed by 2 demises, in Kozhikode (Kerala). The Kerala government reported two deaths. All confirmed cases were males aged between 9 and 45 years and were reported from Kozhikode (Kerala) (fig. 2).[40]

As of 27 September 2023, 1,288 persons who are exposed to infected persons were identified, including healthcare professionals who provided treatment to confirmed cases and who had analyzed the samples. All persons with exposure were quarantined for 21 days. As of September 27, 2023, all 4 cases were found to be clinically stable.[41] The government's action was to declare containment zones in 9 villages in Kozhikode (Kerala), with controlled activity, social distancing, and mandatory use of wearable masks in public. There was a restriction on public large gatherings in Kozhikode (Kerala) till 1 October 2023. Cautions have been sent for neighboring regions to increase monitoring.[42]

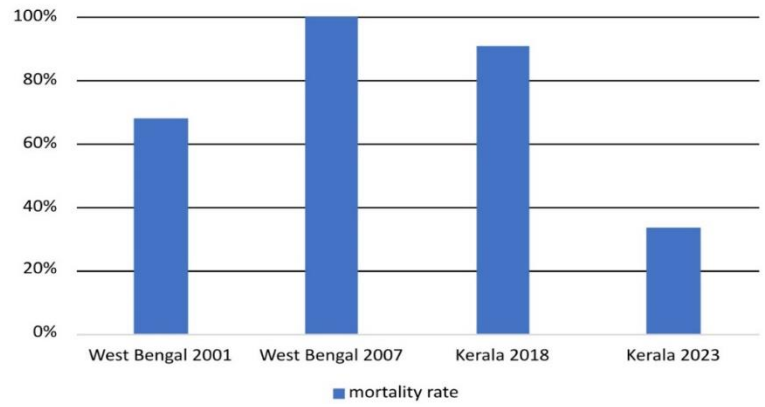

Figure 2: Mortality Rate during Different Outbreak.[42]

PATHOPHYSIOLOGY

The pathological process of NiV infection is the product of a complex interaction between the virus and host immune responses that manifests as a broad spectrum of clinical symptoms and disease consequences. This virus primarily targets respiratory and neurological tissue, leading to severe respiratory distress and a range of neurological symptoms in infected persons.[43] By evading and subverting immune responses, damaging vascular integrity, and arousing inflammatory cascades, the virus is a major factor in the pathogenesis of this disease. Specifics of NiV infection pathophysiology include tissue tropism, inflammatory responses, vascular permeability changes, and immune disruption.[44] These mechanisms must be thoroughly examined to devise effective strategies to cure and prevent NiV. One important characteristic of the Nipah virus in the disease process is its capacity to escape host immunological responses (fig. 3). The virus can suppress immune signaling pathways, decrease antigen presentation, and alter inflammatory responses, which allows for viral reproduction and dissemination within the host. Furthermore, NiV-induced immune evasion pathways can help create long-lasting infections in host tissues including the brain, which could result in late-onset and relapsed encephalitis.[45]

Particularly in the central nervous system (CNS), NiV infection results in systemic vasculitis with extensive thrombosis and parenchymal damage. The most common histological observations include necrosis,

endothelial cell death, the formation of syncytial giant cells in injured arteries, and characteristic viral inclusions that may be seen under light and electron microscopy.[46,47]

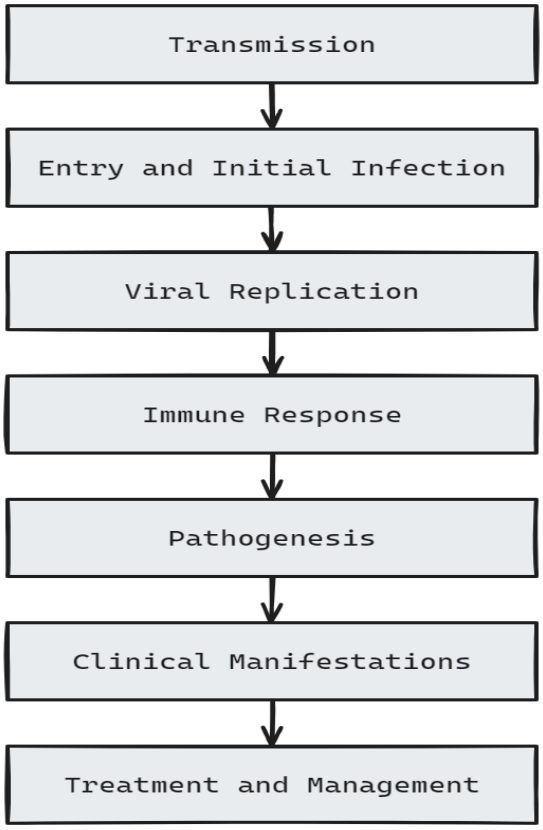

Figure 3: Principal Components of NiV Pathophysiology. [43]

A brief description of the principal components of the NiV's pathogenesis is provided below:

Transmission

Humans develop NiV mostly through direct contact with sick bats or their secretions, such as urine and saliva. Additionally, the intake of infected food products, notably date palm sap, has been linked to several outbreaks. Human-to-human transmission can also happen, especially in clinical settings (fig. 4).[48]

1) Fruit bats are natural reservoirs of NiVes. Fruit bats with NiV consume date palm sap. Viruses can survive in sugar-rich fluids like apple pulp. **2)** The virus is transmitted to people by consuming date palm sap. **3)** Fruit bats (Pteropus spp.), which are NiV reservoirs, spontaneously dropped virus-containing drops on fruit trees, infecting soil and fruits. **4)** Animals, including pigs, consume infected fruits. Pigs act as both intermediate and amplifying hosts. The establishment and transmission of novel lethal zoonotic viral illnesses such as Nipah are facilitated by proximity to fruiting trees, fruits such as date palms, fruit bats, pigs, and people. **5**) Pork meat tainted with NiV is being exported to other regions. **6)** Consuming infected pork can spread the virus to people. **7)** Close contact with an infected individual can spread NiV to others.

Entry and Initial Infection

The NiV enters the body through skin breaches or mucosal surfaces like the respiratory tract. The infection essentially targets resistant cells like dendritic cells and macrophages, where it recreates and spreads to different tissues. NiV primarily targets endothelial cells, epithelial cells, and neurons.[49] The viral entrance process begins with attachment to cellular receptors, specifically the ephrin-B2 and ephrin-B3 receptors, followed by fusion of the viral envelope with the host cell membrane (fig. 5).[50]

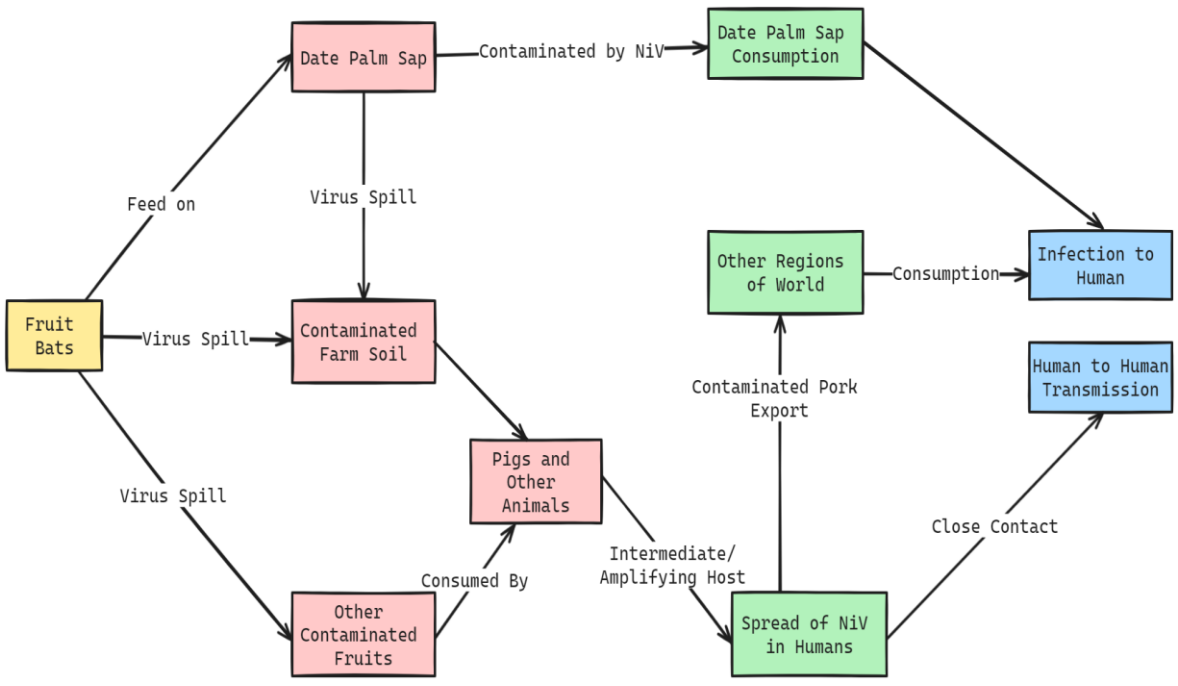

Figure 4: Transmission of NiV.[20]

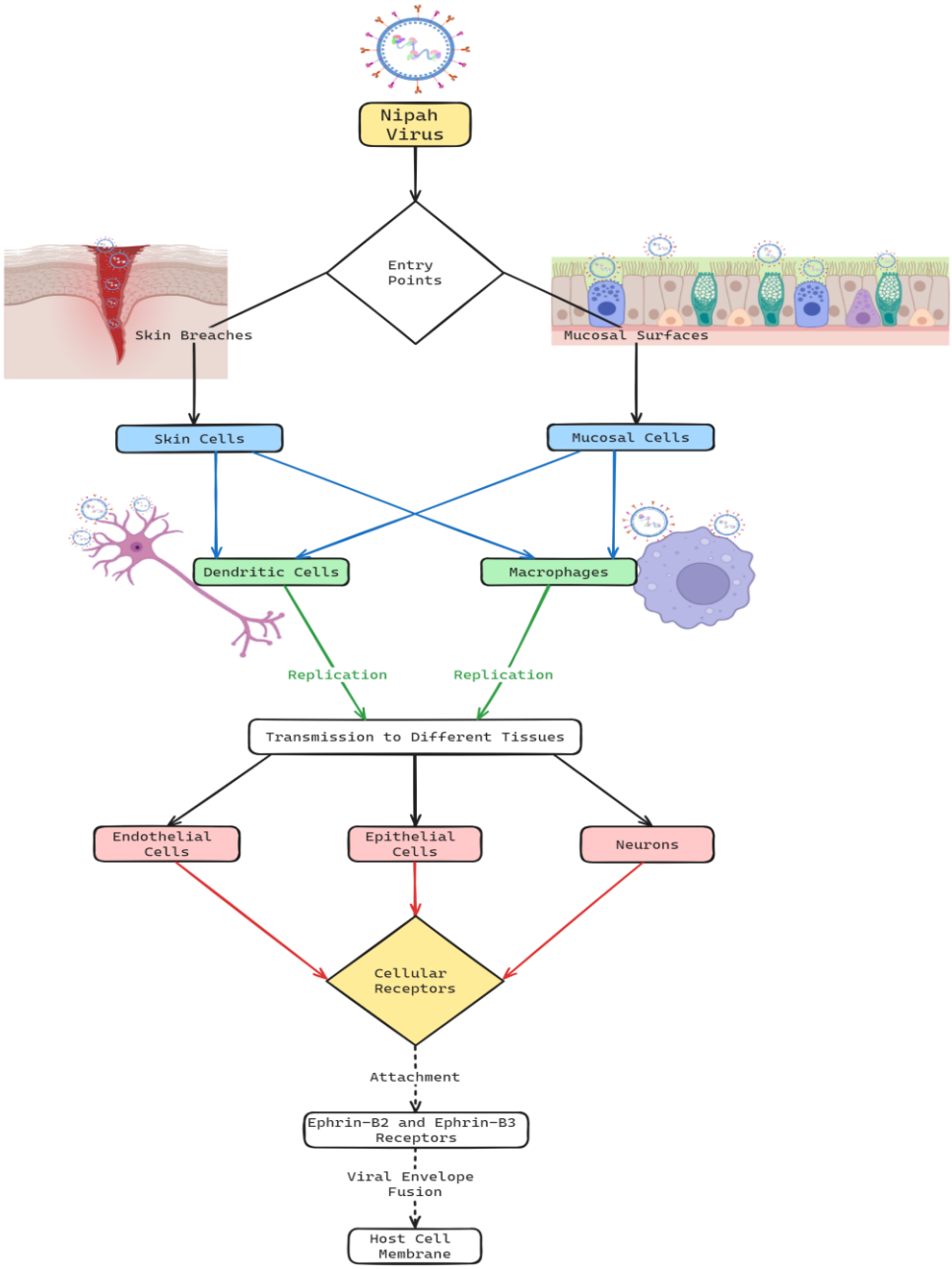

Figure 5: Entry and Initial Infection.[50]

Understanding the entry and initial infection mechanisms of NiV is essential for elucidating the early stages of viral pathogenesis, tissue tropism, and dissemination within the host. By targeting these critical steps in the viral life cycle, researchers can develop strategies to prevent viral entry, limit systemic spread, and mitigate the neurological complications associated with NiV infection.[50]

Viral Replication

Once within the host cells, the NiV uses its RNA genome to replicate and create viral proteins. The virus can reproduce in a variety of tissues, including the respiratory tract, lymphoid organs, and the central nervous system. The virus's rapid reproduction causes the release of a high number of viral particles, which spreads the infection.[19] NiV infection can potentially cause vascular damage, such as endothelial cell dysfunction and disruption of the blood-brain barrier. By unraveling the molecular mechanisms of viral replication, RNA editing, immune evasion, and host-virus interactions, researchers can identify potential targets for antiviral therapies, vaccine development, and strategies to disrupt the replication cycle of NiV (fig. 6).[51]

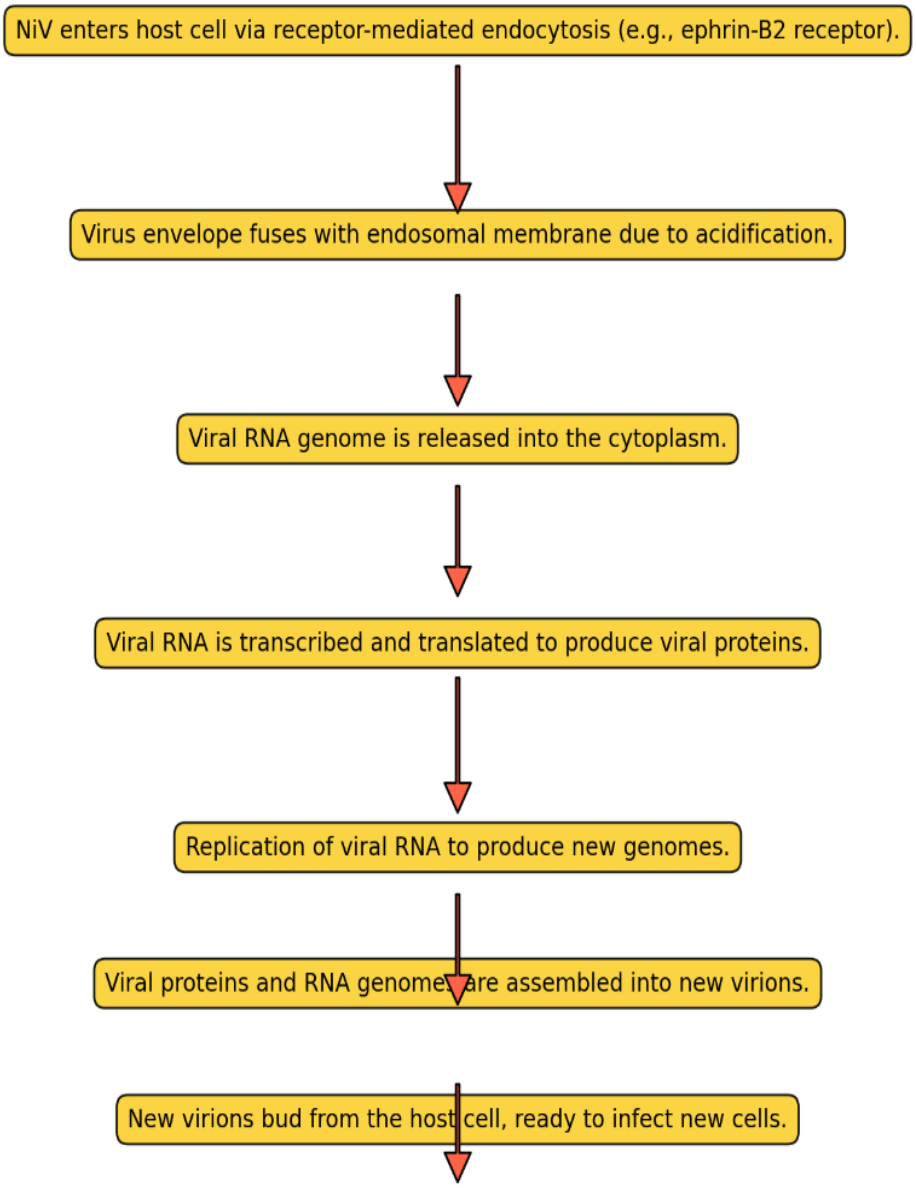

Figure 6: NiV Replication in Host Cell.[43]

Immune Response

The human immune response is critical in the development of NiV infection. The virus may avoid and suppress the host's innate immune response, allowing for unrestricted viral multiplication and dissemination throughout the body. However, an overly strong immune response can lead to tissue damage and disease progression.[52] Initially, the innate immune system detects the virus and initiates a response to restrict its spread. However, NiV has evolved methods to escape and suppress the host's immune response, allowing for unrestricted viral multiplication and spread throughout the body. This dysregulated immune response contributes to the severity of NiV infection.[51] The immune response to NiV infection involves the production of antibodies and the activation of various immune cells to combat the virus. During infection, the body's immune system recognizes the presence of the virus and mounts a defense mechanism to eliminate it.[51]

Overall, the immune response to NiV infection is critical for controlling viral transmission and reducing disease severity (fig. 7). Further research into immune-based treatments, such as monoclonal antibodies, could provide viable therapeutic options for NiV infection. By elucidating the intricate interactions between NiV and the host immune system, researchers can identify potential targets for therapeutic interventions, vaccine development, and strategies to enhance host immunity against NiV infection.[53]

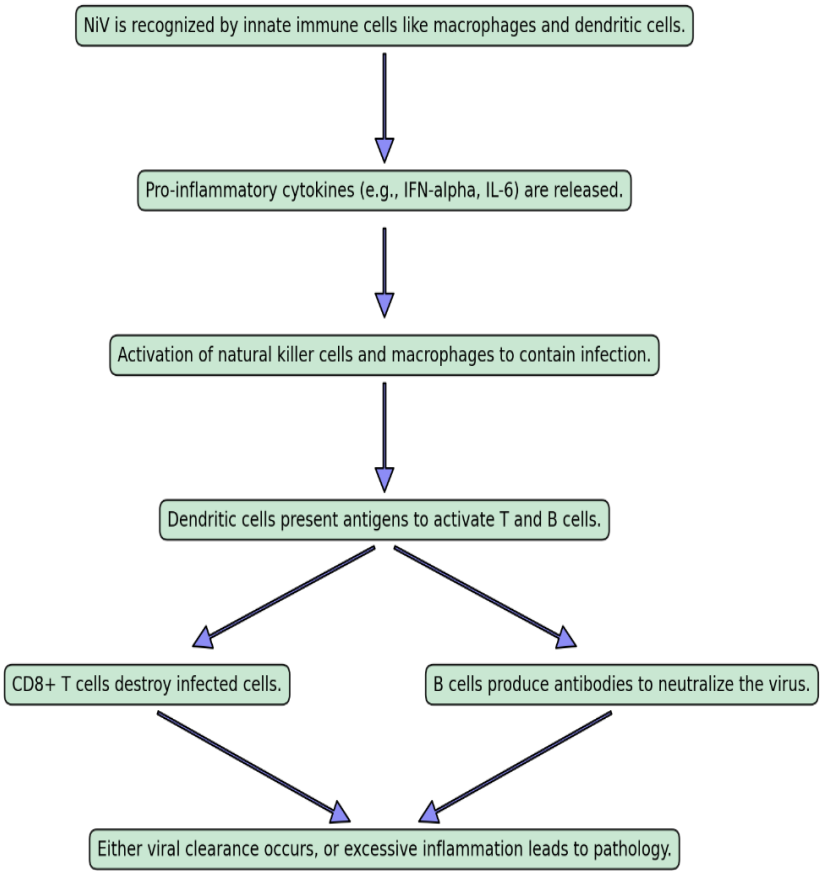

Figure 7: Immune Response towards NiV.[13]

Pathogenesis

Understanding the pathogenesis of NiV infection is critical for establishing effective diagnostic, treatment, and prevention measures for this serious and frequently fatal disease. The interaction between the virus and the host immune system, which sets off a series of events resulting in tissue damage and disease, is central to the pathophysiology of NiV infection.[54] NiV predominantly targets the central nervous system, causing acute encephalitis, which is characterized by inflammation of brain tissue. Furthermore, NiV infection can produce systemic vasculitis and endothelial dysfunction, which can lead to vascular leakage, multiorgan failure, and even death in severe cases (fig. 8).[55]

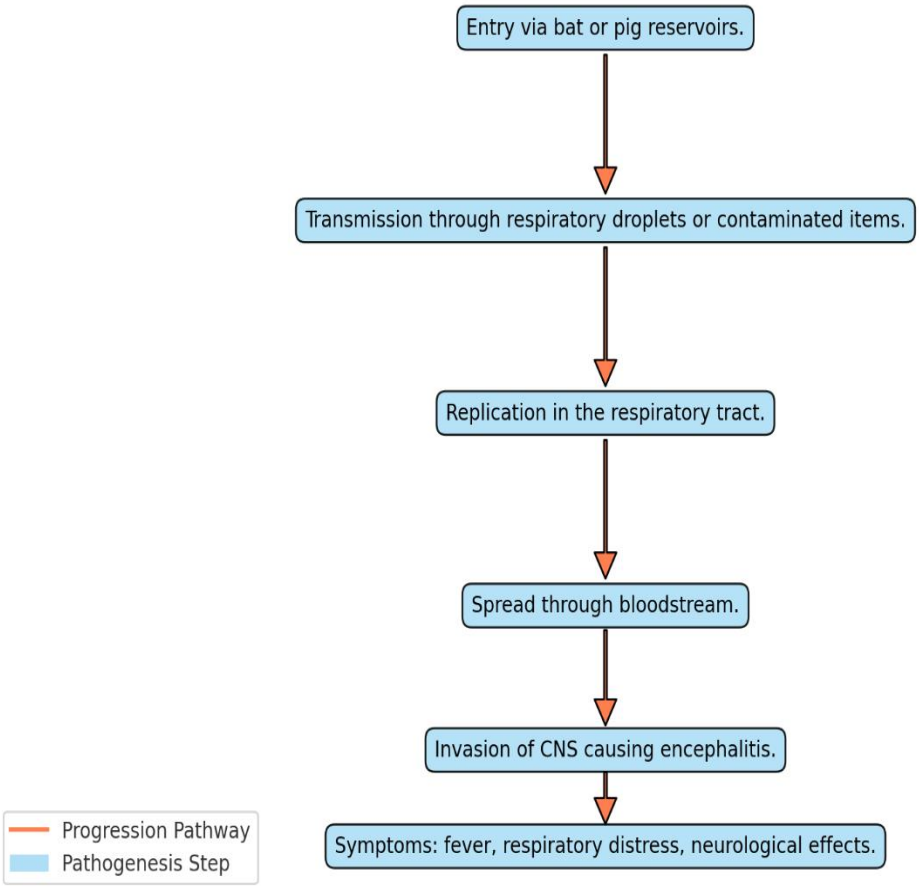

Figure 8: Pathogenesis of NiV.[56]

Clinical Manifestations

The clinical manifestation of NiV infection ranges greatly, from asymptomatic illness to severe respiratory distress, encephalitis, and coma. Fever, headache, drowsiness cough, and altered mental status are among the most common symptoms.[27]

Treatment and Management

There are currently no particular antiviral therapies or vaccinations for NiV infection. The primary mode of treatment continues to be supportive care, which includes respiratory assistance, hydration management, and symptomatic treatment.

TREATMENT

The mainstays of treatment for NiV disease are syndromic management of acute encephalitis syndrome and supportive care. Certain pharmacological solutions should not be considered alternatives to infection control methods in the current context. To justify post-exposure prophylaxis in people who had close contact with confirmed Nipah patients, further data must be gathered.[56] Nonetheless, ribavirin, m102.4 monoclonal antibody, and favipiravir are the three pharmacological alternatives that have been investigated for the potential therapy and post-exposure prophylaxis of NiV infection.[4]

MANAGEMENT

Patients need to be isolated, and strict infection control procedures need to be followed. The mainstay of treatment for NiV infection is supportive breathing, circulation, and airway maintenance. The balance between fluid and electrolyte is preserved. Mechanical ventilation is required for patients who have acute respiratory failure and severe pneumonia. It is preferable to use invasive mechanical ventilation.[47] The treatments which show effect against NiV are-

1. Antiviral drugs.
2. Monoclonal antibodies.
3. Vaccines.

1. ANTIVIRAL DRUG THERAPY

There are few antiviral strategies for the treatment of hernia viruses that have been explored in animal models, and there are no recognized or approved medicines for the treatment of hernia virus transmission in humans. One prominent first line of treatment and management for presumed infections with no established cause of disease is Ribavirin.[57]

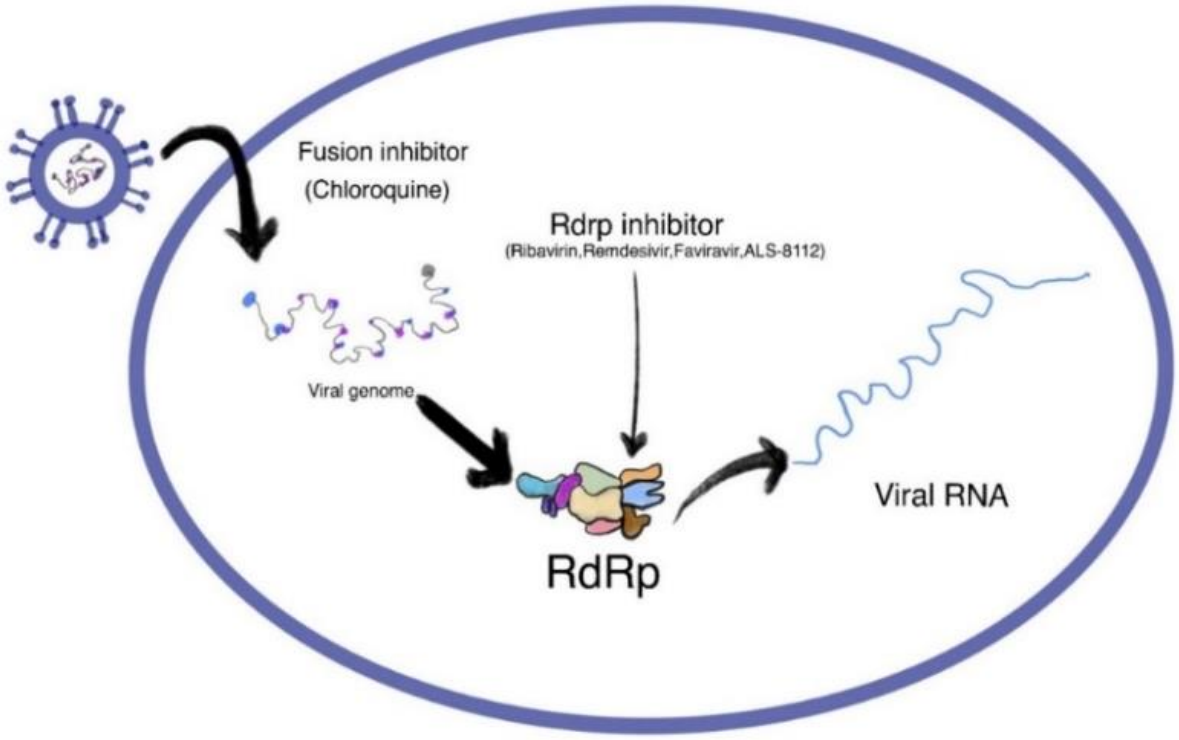

Figure 9: MOA of antiviral drug therapy.[43]

Ribavirin

The prominent 1st line treatment and management for presumed viral infections with an undefined etiology is ribavirin. The antiviral activity of ribavirin is demonstrated against a broad range of RNA and certain DNA viruses and is a recognized or authorized treatment for several viral infections, including arenaviral hemorrhagic fever and respiratory syncytial virus. Ribavirin is effective against the replication of the Hendra and NiVes, according to in vitro experiments.[58]

Chloroquine

In addition, the antibiotic chloroquine has previously been shown to block an important proteolytic process required for the growth and activity of Hendra virus F-glycoprotein. Thus, it should come as no surprise that chloroquine was later demonstrated to prevent Hendra viral infection in cell culture and suppress Nipah.[59] In 2009, ribavirin and chloroquine were given to a single HeV-positive person, but there was no discernible clinical improvement. Three more individuals were given ribavirin.[59] Therapy combined with chloroquine following possible exposure to secretions contaminated with the Hendra virus from horses who were sick. Even though all three people lived, the treatment's effectiveness is still unknown because the infection was not proven.[3]

Remdesivir (used in animals' model)

Remdesivir is a nucleotide analog that has a broad spectrum of antiviral activity against coronaviruses, filoviruses, and paramyxoviruses. Remdesivir was associated with 100% survival in the NiV-B challenge induced by the AMG model, in which daily remdesivir injections were initiated 24 hrs. after infection and continued for 12 days.[60] Out of the four NHPs who were part of the trial, two only had moderate respiratory symptoms, which went away by day 14 after the infection. When the investigation came to an end 92 days after infection, One animal's brain had RNA.[61] Even though these outcomes are very positive, more research is required to fully assess the antiviral effect of remdesivir. Additionally, remdesivir has been listed in a clinical trial for assessing the Ebola treatments in year 2018 epidemic in the Democratic Republic of the Congo. [61] Remdesivir did seem to be safe, even though this study indicated that it was less effective against the Ebola virus sickness than monoclonal antibodies. Lately remdesivir was used to treat SARS-COV-2 patients, but the results are still unknown.[62]

Favipiravir (used in animal models)

Favipiravir is a small purine analog molecule having antiviral properties that is licensed in Japan for the treatment of pandemic influenza. Favipiravir successfully prevented fatal NiV-M infection in the Syrian golden hamster model when administered immediately after infection and daily for 14 days.[63] During the duration of the trial, no pathological alterations in tissues or viral RNA were found, and no single animal who had received treatment exhibited any kind of clinical symptoms of illness. Future research is required to assess favipiravir's post-exposure antiviral effectiveness.[64]

Griffithsin (used in animals' model)

Clinical studies are now evaluating the homodimeric high-mannose oligosaccharide-binding lectin Griffithsin (GRFT) as a topical antiviral agent against HIV-1. A synthetic trimeric tandemer (3mG) and an oxidation-

resistant GRFT(Q-GRFT) showed antiviral efficacy for NiV in the nanomolar range in cell culture investigations. The preventive potential of Q-GRFT and 3mG was assessed in the Syrian hamster model, yielding complete chances of survival of 35% and 15%, respectively. More research is needed to further evaluate and development of Q-GRFT for prophylaxis of NiV virus.[65,66]

2. MONOCLONAL ANTIBODIES

Currently, the most hopeful treatment by monoclonal antibody for NiV infection in humans is cross-reactive monoclonal antibody (mAb) m102.4. This particular antibody was by preventing G from interacting with the host cell Ephrin B2 and B3 receptors, establishing a functional relationship between NiV and HeV binding glycoprotein G having the ability to counterbalance both.[6667] The protective action was observed in non-human primates and ferrets against HeV with the use of m102.4 monoclonal antibody. In the ferret model of illness, upon infusion of a single dose of m102.4 antibody intravenously for 10 hrs. absolute immunity was observed. It also shows absolute prevention of intranasal transmission in ferrets' models.[67] Even more encouraging were post-exposure experiments conducted using the African Green Monkey (AGM) paradigm. M102.4 antibody shows absolute prophylaxis despite the onset of clinical symptoms and the presence of the virus in the blood in AGMs models, m102.4 shows absolute prophylactic effects until 3 days after NiV transmission and 5 days after NiV-M transmission.[68,69] Two days following the first dosage, a second one was given in both trials. Remarkably, research that shows contrast between the pathogenesis of NiV-M and NiV-B in the African green monkeys recommends, that NiV-B could have a smaller treatment window than NiV-M. Only when given up to three days after NiV-B infection did m102.4 show protective effects, which is consistent showing earlier inception of lethal illness in NiV-B when collated with NiV-M. Animals with the infection that received the first therapy five days after the infection died from the illness.[70] The use of m102.4 in humans for sympathetic purposes and in a clinical trial (Phase-I) was supported by the findings of these investigations. So far, 14 doses of m102.4 have been administered as sympathetic treatment with subsequent hazardous exposure to HNVs, with zero documented adverse effects linked to the medication in any of the following reported cases. Moreover, none of the recipients who had received antibody doses experienced sickness, though it's unclear whether this was due to the m102.4 therapy. The evaluation of m102.4's safety, tolerability, and immunogenicity in healthy humans resulted from a phase I clinical trial, which combined compassionate therapy for post-exposure treatment with encouraging preclinical evidence from animal research.[57]

3. VACCINES

Because there are no proven treatments for NiV and it is more widely distributed, there is a considerable health risk. Developing vaccinations to stop NiV infection might stop it from spreading, especially in more susceptible communities. Generating the principal reservoir of the virus, bats provide practical problems when it comes to vaccine development since handling live infections has additional hazards related to biohazards.[71] Inactive pathogens are frequently used as antigens in conventional vaccinations; however, researchers prefer different kinds of antigens to minimize the danger of biohazard. Subunit vaccines, which employ pieces of glycoprotein to elicit the defensive immunological response, are one potential strategy. For example, when given subcutaneously to cats, soluble G glycoprotein by oneself stimulates the development of antibodies that neutralize the serum. For up to two months, vaccinated cats had noticeably greater antibody levels (titer - 20000).[72] Comparably, the Hendra virus subunit glycoprotein (HeVsG) showed remarkable effectiveness in shielding ferrets from disease and inhibiting NiV reproduction, protecting a minimum of 14 months following vaccination. HeVsG treatment, however, forms antibodies against the Nipah virus in pigs, albeit they did not stretch out to prophylaxis levels. After the post-challenge of 5-7 days, animals had an 80% increase in no cross-neutralizing antibodies, but they were deficient in meaningful cell-mediated immunity and prevention.[73] It's interesting to note that pigs exposed to NiV orally and nasally had a protective antibody response as well as a cell-mediated immune response.[73] HeVsG administration, on the other hand, protected against NiV infection in AGMs. The titer of 2650 of serum-neutralizing antibody was noted on Day 14 post-inoculation; this titer decreased after 28 days. When challenged, no one of the animals administered with the vaccine displayed any kind of symptoms of virus exposure, viral replication, or pathology. The recombinant subunit vaccine's effectiveness in non-human primates encourages its continued preclinical study for possible use in humans.[74,75]

Table 1. List of Candidate Vaccines.[76]

CANDIDATE VACCINE	ADVANTAGES	DISADVANTAGES	CLINICAL STAGES
Recombinant measles vires	Genetically stable	Pre-existing immunity	Preclinical
Recombinant vaccinia virus	Reversion of pathogenicity does not observe	Pre-existing immunity	Preclinical
rVSV	Third-generation vaccine against smallpox. Safe and effective viral vector	Highly immunogenic	Preclinical

Recombinant rabies virus	Promising candidate Robust immune response	Highly immunogenic	Preclinical
AAV	Lack of pathogenicity Ability to express recombinant protein in good quantity	Pre-existing immunity	Preclinical
ChAdox1-vectored vaccine	Generates protective immune response	Pre-existing immunity	Preclinical
Newcastle disease vaccine	Replicates in high titre	Insufficient data	Preclinical
Canarypox virus based vaccine	Pre-immunity does not exist	Insufficient data	Preclinical
m RNA	Pre-immunity does not exist High neutralizing titre	Less stable than DNA vaccine	Phase 1 (for mRNA-1215)
mAb	High neutralizing titre	Chance of ADCC	Phase 1(for m102.4)

CONCLUSION

The Nipah Virus (NiV) represents a significant zoonotic threat, demonstrating the potential for interspecies transmission and severe pathogenicity. Initially identified in fruit bats of the Pteropus genus, NiV's emergence highlighted the dynamic nature of viral spillover events and their implications for public health. NiV's tropism for respiratory and neurological tissues underscores its ability to cause devastating illnesses in both humans and animals. The virus's transmission mechanisms, including ingestion of fresh date palm sap and potential indirect transmission via domestic animals, underscore the complexity of its ecological interactions and potential for continued spread. Despite advancements in understanding NiV's pathogenesis, therapeutic options remain limited, emphasizing the critical need for antiviral interventions and vaccines. Current management strategies primarily focus on supportive care, hydration, and respiratory support, reflecting the challenges posed by the absence of specific therapeutic agents. Ongoing research into antiviral compounds such as ribavirin, favipiravir, and m102.4 monoclonal antibodies offers promise for potential treatment and post-exposure prophylaxis. However, the lack of definitive solutions underscores the urgency of continued surveillance, research, and collaborative efforts across scientific disciplines and international borders. As we navigate the intricacies of NiV and its broader implications for zoonotic disease dynamics, proactive measures in surveillance, response preparedness, and public health education are essential in mitigating the impact of this formidable viral pathogen on global health security.

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