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Therapeutic Advancement in Treatment and Prevention of Nipah Viral Infection: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The Nipah virus (NiV) is an emerging zoonotic pathogen that poses a major risk to global health, with a high mortality rate and the potential for wide outbreaks. NiV, which originated in fruit bats, has shown a concerning potential to infect humans and cause serious respiratory and neurological disorders. The virus has a pleomorphic structure and a broad host range, preventing efforts to understand and regulate its pathogenesis. This review discusses current advances in the

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prevention and management of NiV, including the efficacy of several antiviral therapies *in vitro* and *in vivo*. Treatments such as Ribavirin, Favipiravir, Acyclovir, Remdesivir, and Balapiravir have produced varying results, whilst monoclonal antibodies such as m102.4, h5B3.1, and nAH1.3 provide effective neutralization but require additional testing in humans. In addition, innovative vaccination techniques such as recombinant measles virus, subunit vaccines, vector vaccines, and the novel mRNA-1215 vaccine have shown success in preclinical and early clinical trials. To reduce the risk of human transmission, preventive measures include early outbreak detection through improved surveillance systems, exposure-based screening, and educational activities. This covers vital guidelines like avoiding raw date palm sap during outbreak seasons and using physical barriers to prevent bat-to-human transmission, which is vital for controlling this deadly virus.

Keywords: Nipah virus (NiV); antiviral therapies; monoclonal antibodies; vaccine development; preventive measures.

1. INTRODUCTION

Nipah Virus (NiV) is a zoonotic emergent with high mortality rates. It is classified as a Biosafety Level 4 pathogen and is considered a priority by the World Health Organization (WHO). This classification is due to its tendency to cause outbreaks and the current absence of approved therapeutic or vaccine options for human use [1,2]. The Nipah virus, classified as an RNA virus within the Paramyxoviridae family, was initially identified as a zoonotic pathogen after the occurrence of outbreaks in Malaysia and Singapore between 1998 and 1999 [3]. These outbreaks resulted in the manifestation of severe respiratory illnesses in pigs and encephalitic symptoms in humans. Moreover, it is worth noting that this virus has posed major public health challenges across various regions in Asia. The Nipah virus, classified as a paramyxovirus, falls under the Henipavirus genus within the Paramyxovirinae subfamily, which is part of the larger Paramyxoviridae family. It also belongs to the Mononegavirales order [3]. The Nipah virus (NiV) is classified as a negative-sense, single-stranded, enveloped RNA virus [3]. The viral isolations obtained from various sources have provided evidence of the existence of two distinct strains of the Nipah virus, namely NiV-M (originating from Malaysia) and NiV-B (originating from Bangladesh) [4]. The characteristics exhibited by these two strains help to clarify the differences in terms of lethality, infectivity, and pathogenesis that have been observed in human cases during outbreaks [5,6]. The human cases observed during the outbreak in Malaysia-Singapore are exclusively associated with the NiV-M variant, while the outbreaks documented in Bangladesh and India are linked to the NiV-B variant. This pattern highlights the occurrence of multiple viral emergences from the natural reservoir, namely the Pteropus species, commonly known as Flying foxes in India and Bangladesh, to humans [4]. This review aims to address crucial information gaps by integrating existing research on the virological characteristics, transmission dynamics, epidemiological trends, and preventative measures of Nipah virus infection (NiV). The emphasis is on identifying gaps in current therapeutic and preventive strategies, as well as vaccine development efforts, and advocating for a comprehensive global health strategy to develop effective interventions that can be applied universally across various geographical and socioeconomic contexts.

1.1 Transmission

During the outbreak in Malaysia-Singapore, it was observed that transmission of the virus occurred only from pigs to humans. In contrast, outbreaks in Bangladesh and India have consistently shown evidence of transmission between humans [4]. These observed differences may potentially be associated with the involvement of the respiratory system and its impact on the ability of the virus to spread, as well as the specific properties or genotypes of the viral strains [4]. Additionally, variations in the baseline health status of patients, disparities in healthcare provision, and other unidentified factors could also contribute to these differences [7]. The transmission of NiV from Pteropus spp. to humans necessitates the presence of an interaction interface that facilitates the emergence of the virus from its natural reservoir. One of the primary factors contributing to outbreaks in Bangladesh is the consumption of fresh palm sap and its derived products. This source of contamination plays a significant role in the majority of reported cases [8].

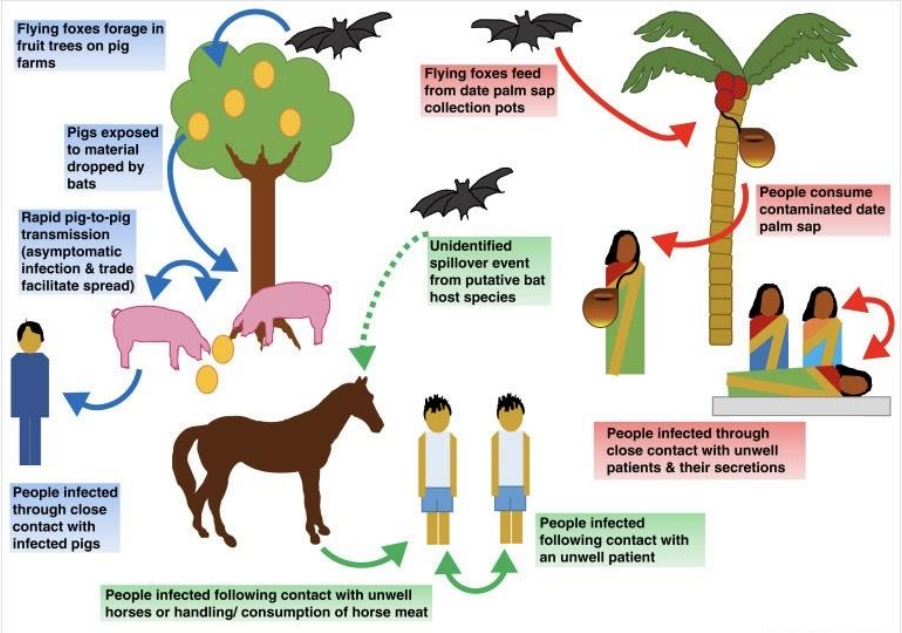

Fig. 1. Transmission of Nipah virus

1.2 Incubation

According to the available data, it has been observed that the median incubation period of individuals who were exposed to a single case of Nipah virus is approximately nine days, with a range of 6 to 11 days [9]. However, it is important to note that the time interval between exposure and the onset of illness can vary between 6 to 16 days, as reported in previous studies [10,11,12,4]. According to research conducted in Bangladesh, it has been determined that the median incubation period from the time of consuming raw date palm sap to the onset of illness is 7 days. The observed range for this incubation period is between 2 and 12 days [9].

1.3 Pathophysiology

The outer viral surface is characterized by a pleomorphic extracellular bilayer, within which the attachment (G) and fusion (F) proteins are embedded. The inner surface of the viral capsid is determined by the arrangement of matrix proteins (M). These matrix proteins are responsible for maintaining the structural integrity of the capsid. Additionally, the capsid contains various viral proteins such as nucleocapsid proteins (N), phosphoproteins (P), and the large RNA polymerase enzyme (L) [5,6,4]. These proteins play crucial roles in the replication and transcription processes of the viral RNA strand, which is attached to them. The virus is known to enter the respiratory tract through two primary modes of transmission: aerosol transmission and respiratory droplets. Upon establishing themselves within the upper and lower respiratory epithelium, virus particles can infiltrate the epithelial cells through a mechanism known as membrane fusion. The interaction between the head region of the tetrameric G attachment glycoprotein and the cellular surface Ephrin B2/B3 receptors has been observed [5,6]. Additionally, it has been found that the C-terminal portion of the G glycoprotein activates the trimeric F fusion glycoprotein. The F protein is composed of two hydrophobic domains that come together to form a six-helical bundle. This bundle can penetrate the host cell membrane, which in turn triggers the process of membrane fusion. Once fusion occurs, the virus can replicate itself using the machinery of the host cell [13]. The localization of F and G viral glycoproteins in the basolateral membranes of host cells facilitates the spread of the virus by facilitating fusion of the host cell membrane with neighboring epithelial cells, resulting in the formation of distinct cellular syncytia [13].

The process of systemic dissemination occurs through the mechanism of viral budding and subsequent release. This process plays a crucial role in the virus's ability to spread to the mucosal-associated lymphoid tissue (MALT) and establish attachment to host leukocytes [13]. These events collectively facilitate the virus's

entry into the bloodstream, enabling its further dissemination throughout the body [13]. NiV and Pteropus spp. are thought to have co-evolved for centuries, hence it is anticipated that NiV has developed evasion mechanisms against Pteropus immune responses. As a result, the excellent interspecies immunity conservation observed in animals may help to explain the virus's broad infectious range. NiV inhibits the synthesis and release of cytokines, including IFN type 1 α/β, CCL4, CCL5, and TNF-α. The W protein, generated from the P gene, has the highest inhibitory potential against IFN type 1 α/β gene production in host cell nuclei [14].

1.4 Clinical Presentations

The acute phase of Nipah virus infection is characterized by the beginning of rapid advancing encephalitis, which is frequently accompanied by respiratory complications like atypical pneumonia and disseminated vasculitis [9]. After an incubation period that usually lasts from 7 to 11 days, individuals may manifest symptoms resembling those of influenza, such as a fever ranging from moderate to high-grade, cognitive changes, difficulty breathing, and a cough. Following the initial decline in neurological and respiratory function, a subsequent deterioration occurs, resulting in the development of various conditions including encephalitis and acute respiratory distress syndrome (ARDS) [4,9]. The culmination of this multisystemic failure ultimately leads to mortality, typically observed within an average duration of six days following the manifestation of symptoms. The primary cause of death is attributed to the involvement of the brainstem. Estimates indicate that the mortality rate is approximately 75%, and it is worth noting that asymptomatic cases are infrequent [15]. Moreover, it has been observed that individuals who have survived an infection caused by the Nipah virus frequently encounter enduring neurological deficits. Approximately 22% of these survivor's report experiencing residual neurological impairment [15,9]. One should take note of the significant difference in the clinical presentation observed between the Malaysia-Singapore outbreak and the subsequent outbreaks in Bangladesh and India. The former outbreak displayed a conspicuous lack of respiratory involvement, while respiratory conditions emerged as a prevalent characteristic in the subsequent outbreaks. This discusses the severe clinical ramifications associated with Nipah virus infection, thereby underscoring the pressing necessity for the development and implementation of efficacious preventive interventions and therapeutic modalities to effectively counteract the deleterious effects of this exceptionally virulent pathogen [15,9].

2. METHODOLOGY

This study conducted a comprehensive review search of the electronic database PubMed to identify relevant articles pertaining to

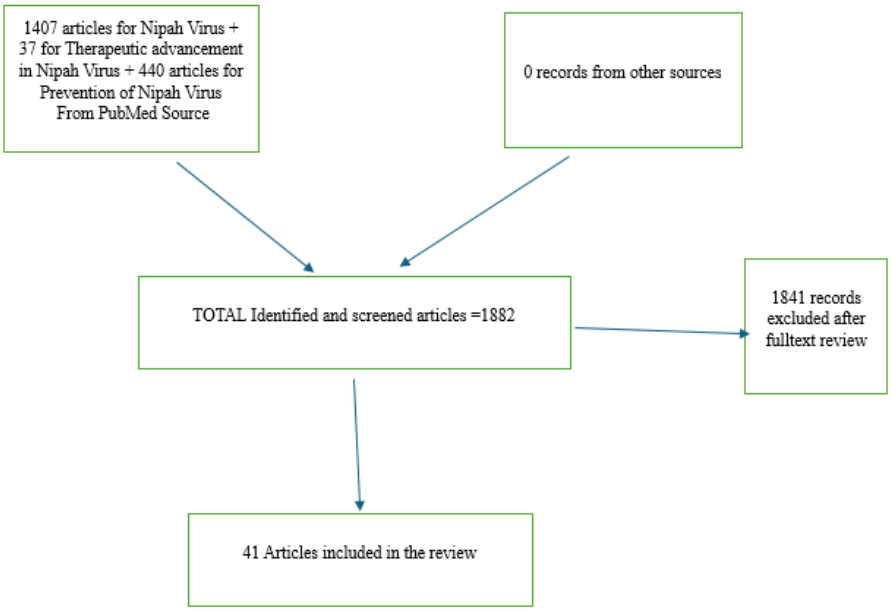

Fig. 2. Flow chart showing study protocol

the topics of "Nipah Virus," "Therapeutic Advancement in Nipah Virus," and "Prevention of Nipah Virus." The search was conducted retrospectively, encompassing articles available until March 2024. The study identified a total of 1882 articles, specifically 1407 articles focused on Nipah Virus, 37 articles on Therapeutic advancement in Nipah Virus, and 440 articles on Prevention of Nipah Virus. Among the pool of 1882 articles that were initially identified, a total of 1713 articles were excluded from the study due to their lack of relevance to the research focus. Additionally, 128 articles were found to have overlapped results, further reducing the number of articles eligible for inclusion. Ultimately, only 36 articles met the criteria and were included in the study. The risk of bias in each study was evaluated using the Cochrane Collaboration's tool, as outlined in the Cochrane Handbook.

3. RESULTS AND DISCUSSION

As part of our continuous endeavors to counteract the Nipah virus (NiV), a variety of therapeutic and preventive strategies have been investigated, each providing distinct perspectives on the management of the virus. The exploration of diverse antiviral therapies unveils a multitude of challenges and significant achievements. As an example, the antiviral drug Ribavirin was utilized as a treatment option during the outbreak that occurred in 1998. Its administration resulted in a significant reduction in mortality rates, specifically by 36%. Nevertheless, the ongoing discourse persists concerning the overall efficacy of viral combat strategies, thus emphasizing the complex nature of this subject matter. Favipiravir, a pharmaceutical compound, has demonstrated encouraging outcomes in live animal models, exhibiting a remarkable 100% survival rate. This finding instills optimism and raises prospects for potential advancements in therapeutic interventions in the future.The administration of Acyclovir during the 1999 Singapore outbreak resulted in a favorable outcome for most patients who received the treatment. However, the precise effectiveness of Acyclovir against NiV remains uncertain, focusing on the necessity for further investigation and research. Remdesivir, a drug recognized for its efficacy in previous viral outbreaks, has exhibited a noteworthy 67% survival rate when administered in the early stages of treatment to African green monkeys. This finding implies that the drug holds a guarantee for potential therapeutic application if administered promptly. The potential effectiveness of Balapiravir has been demonstrated in controlled laboratory environments. However, further validation through real-world testing is necessary to ascertain its efficacy in practical settings.

When it comes to monoclonal antibodies, m102.4 stands out for its substantial NiV neutralizing activity, which represents a significant advancement in post-exposure treatment choices. Humanized antibodies like as h5B3.1 and the widely neutralizing nAH1.3 are being developed to target different components of the virus and strengthen our defenses against prospective outbreaks. Vaccination attempts are also progressing, with numerous options, including recombinant VSV-vectored, subunit, and vector vaccines, demonstrating protective effects in animal tests. The mRNA-1215 vaccine, which is currently in Phase 1 studies, shows promise for human use, potentially changing the landscape of NiV prophylaxis. Additionally, the concept of passive vaccination via polyclonal serum is being investigated to provide instant defense mechanisms. On the preventative front, we prioritize early detection and containment, using population surveillance systems and exposure-based screening to slow the spread. Educational efforts are essential particularly in endemic areas, where public awareness and behavior modification can significantly reduce transmission risks. These measures include cautioning against consuming raw date palm sap and encouraging the use of physical barriers to reduce human-bat contact during critical periods.

3.1 Advancement in Treatments

3.1.1 Anti-viral therapy

Ribavirin: The open-label trial led by Chong HT et al. found a 36% drop in death rates with Ribavirin therapy, with no reported side effects. Ribavirin emerged as the key pharmaceutical intervention during the 1998 NiV outbreak, owing to its broad antiviral activity against both DNA and RNA viruses [16]. However, results from a NiV-infected hamster model demonstrated that Ribavirin only delayed mortality, implying that the observed decrease in human mortality during the same outbreak could be ascribed to better patient care and practical treatments rather than Ribavirin's single action [17]. A subsequent analysis of the 1998 outbreak, which included 94 patients with epidemiologically and clinically proven NiV infections, found that Ribavirin was

used in 78% of cases but was not associated with a significant reduction in fatality rates [10].

Favipiravir: is a ribonucleotide analog, is known for its ability to specifically target the viral RNA polymerase enzyme. By doing so, it effectively inhibits the replication and transcription processes of RNA viruses, resulting in broad-spectrum antiviral effects [11]. According to a study conducted by Dawes BE et al., it was demonstrated that the drug, when administered orally in *in vivo* simulation models using hamsters, at a dosage of 300 mg/kg/day twice daily, did not lead to any observed morbidity and resulted in a 100% survival rate [18].

Acyclovir: a guanosine analogue and was administered empirically to nine abattoir workers diagnosed with encephalitis during the March 1999 NiV outbreak in Singapore. These workers had also tested positive for NiV IgM. In addition to acyclovir, ceftriaxone was also used as a treatment option. Among the individuals under study, a total of eight individuals managed to survive. However, it remains uncertain whether the usage of acyclovir played a role in their survival [10]. Insufficient published research exists regarding the effectiveness of acyclovir against NiV, both *in vitro* and through additional *in vivo* trials.

Remdesivir: According to a study conducted by De Wit E et al. in 2023, it was found that African green monkeys, when administered Remdesivir at a dosage of 10mg/kg three days after being inoculated with the Nipah virus, exhibited a survival rate of 67%. The findings of this study indicate that the timely administration of Remdesivir during the early stages of Nipah virus infection plays a pivotal role in determining its efficacy, mirroring its current application in individuals afflicted with COVID-19. The proposition suggests that Remdesivir could potentially provide the greatest benefits to individuals diagnosed with the Nipah virus during the initial phases of the illness. Furthermore, it may be worth considering the administration of a higher dosage of Remdesivir in order to improve the effectiveness of the treatment [19].

Balapiravir: The nucleoside analogue, R1479 (balapiravir), has demonstrated considerable potential *in vitro* as an effective treatment against NiV. However, further research is required to evaluate its efficacy *in vivo*. The study exhibited antiviral effectiveness against both Nipah virus (NiV) and Hendra virus (HeV), as evidenced by EC50 values of 4 μM and 2.25 μM, respectively [20].

Antiviral Therapies for Nipah Virus Infection:

a. Acyclovir

Route of Administration: Oral, Intravenous (IV), Topical

Clinical Trials & Research: Used empirically during the 1999 NiV outbreak in Singapore. Limited clinical trial data specifically against NiV.

Applied Cases: Primarily used in Singapore outbreak, with limited documented success.

Recovery Rates: Survival in majority of the treated cases, though direct correlation to Acyclovir is unclear.

Side Effects: Possible renal impairment, requiring dose adjustments.

Pros: Readily available and well-understood profile.

Cons: Uncertain efficacy against NiV, potential renal side effects.

b. Ribavirin

Route of Administration: Oral, IV

Clinical Trials & Research: Extensively used during the 1998 outbreak in Malaysia with documented efficacy.

Applied Cases: Widely used in past outbreaks with documented reductions in mortality.

Recovery Rates: Shown to reduce mortality by up to 36%.

Side Effects: Anemia and other hematological side effects.

Pros: Demonstrated efficacy in reducing NiV-related mortality.

Cons: Significant risk of anemia, requiring careful management.

c. Balapiravir

Route of Administration: Oral

Clinical Trials & Research: Currently lacks *in vivo* data for NiV; efficacy demonstrated only *in vitro*.

Applied Cases: Not yet applied in human cases for NiV.

Recovery Rates: Not applicable.

Side Effects: Data not available.

Pros: Promising *in vitro* results.

Cons: Absence of clinical trial data and unknown side effects.

d. Remdesivir

Route of Administration: IV

Clinical Trials & Research: Shown a 67% survival rate in African green monkeys when administered early during infection.

Applied Cases: Used in animal models with promising outcomes.

Recovery Rates: Promising animal model results suggest potential human application.

Side Effects: Potential hepatic or renal impairment, requiring dose monitoring.

Pros: High efficacy in early intervention models.

Cons: High cost, and intravenous administration might limit its use.

3.1.2 Monoclonal antibodies

m102.4: A strong human monoclonal antibody targeting the G viral glycoprotein-Ephrin B2/B3 interaction surface was discovered by screening G-soluble glycoprotein form antibody libraries. Affinity maturation occurred after light chain rebuilding and random mutation of heavy chain variable areas [12,21]. From 2010 until 2017, this monoclonal antibody, known as m102.4, was humanely delivered to people at high risk of Hendra virus (HeV) or Nipah virus (NiV) infection in Australia, the United States, and India. Notably, these people showed no evidence of infection or harmful health effects after receiving the monoclonal antibody. The use of m102.4 in humans without clinical trials or regulatory authority, such as FDA endorsement, highlights the critical need for treatments and countermeasures against highly pathogenic henipaviruses, which have high mortality rates ranging from 50% to 100% [22]. *In vitro*, m102.4 has considerable neutralizing efficacy against all NiV and HeV strains. Furthermore, it's *in vivo* efficacy against deadly NiV dosages has been demonstrated in African Green Monkey and ferret experimental models, even when provided therapeutically after clinical symptoms and virus discovery. For example, the monoclonal antibody maintains appropriate stability *in vivo*, with biological activity lasting up to eight days after infusion in animal models. Despite its compassionate use in people since 2010 for post-exposure treatment against NiV and HeV in the United States, India, and Australia, the true efficacy of m102.4 in humans is unknown [22].

h5B3.1: A monoclonal antibody was developed to specifically target the F virus glycoprotein's prefusion conformation. It is designed to inhibit virus adhesion to host cell membranes and prevent viral penetration by binding to quaternary F glycoprotein epitopes. This antibody is being studied as a potentially effective option for post-exposure therapy and viral infection prevention. However, *in vivo* investigations are needed to validate its efficacy and safety profile [22].

nAH1.3: A widely neutralizing antibody has been found that disrupts the F fusion-triggering pathway, similar to m102.4, and has comparable efficacy. These antibodies target unique antigenic sites that do not compete with one another. The combination of these antibodies may provide a synergistic therapy strategy, potentially enhancing therapeutic efficacy against Nipah virus infection [23].

Several more monoclonal antibodies have been produced, targeting diverse epitopes and demonstrating promising promise for neutralizing the highly pathogenic Nipah virus (HNV) by inhibiting its attachment to host cells. These antibodies include h1F5, h12B2, Nip GIP35, Nip GIP1.7, HENV26, HENV32, 4H3, 2D3, 1H8, 1F2, 1F3, 4B8, 1A9, 2B12. However, their safety and efficacy characteristics will require *in vivo* testing in the near future to establish their clinical relevance and potential for future clinical application [24].

3.1.3 Chloroquine

In vitro investigations showed that the antimalarial medication chloroquine was highly effective, both alone and in combination with ribavirin. However, chloroquine was ineffective in *in vivo* NiV infection models involving hamsters, ferrets, and AGMs [25,26].

Table 1. Various available Monoclonal Antibody therapy

Monoclonal Antibody	Target	Mechanism
m102.4	G viral glycoprotein–Ephrin B2/B3 interaction	Blocks interaction between G glycoprotein and Ephrin B2/B3 receptors
h5B3.1	Prefusion conformation of F viral glycoprotein	Prevents virus-host cell membrane attachment and viral penetration
nAH1.3	F fusion-triggering mechanism	Interferes with the fusion-triggering mechanism of the F glycoprotein

Table 2. Comprehensive Overview of Vaccination Strategies for Nipah

Vaccine Type	Description	Developmental Stage	Advantages	Disadvantages	Clinical Trial Data	Application Potential
Recombinant Measles Virus (rMV) Vaccine	Utilizes a recombinant measles virus as a vector for Nipah antigens	Preclinical	Strong immunogenicity; possibility for large-scale vaccination campaigns	Safety and efficacy in humans need to be established	Ongoing animal studies to assess immunogenicity and safety	If proven safe and effective, there is potential for widespread use in endemic places.
Subunit Vaccines	Utilizes epitopes or viral peptides of Nipah antigens	Preclinical	Highly specialized immunological response; simple to manufacture; potentially low-cost	Requires identification of optimal antigens; efficacy in humans needs to be confirmed	Studies focusing on identifying the most effective antigens	Ideal for designed immunization strategies after efficacy is demonstrated.
Vector Vaccines	Attenuated virus expresses Nipah antigens.	Preclinical	Induces a serological reaction; potential for mass vaccination	Safety and efficacy in humans need to be established	Early development stages focusing on dosage and immune response	High potential for community-wide immunity in outbreak-prone locations, pending safety confirmation
mRNA-1215 Vaccine	Utilizes mRNA encoding Nipah antigens	Phase 1 Clinical Trials	Rapid development; potential for customized vaccines	Safety and efficacy in larger populations need to be confirmed	Initial human trials to test safety and preliminary efficacy	Excellent technology for quick deployment during outbreaks if testing demonstrate safety and efficacy
Passive Immunization	Administers polyclonal serum against Nipah antigens	Experimental	Immediate immunity with potential for post-exposure prophylaxis.	Logistical challenges in administration and production	Undergoing experimental evaluation to determine effectiveness and optimal usage	Could be an important rapid defense in suppressing unexpected outbreaks

3.1.4 Fusion Inhibitory Peptides

Cholesterol-tagged fusion-inhibitory peptides: This design, which features a cholesterol tag to guide peptides to the target host cell membrane, is intended to prevent F glycoprotein conformational changes that are required for viral pore-mediated host cell penetration. In Golden Hamster experimental models, concurrent administration and viral inoculation resulted in an 80% survival rate against lethal virus dosages, demonstrating increased drug penetration and concentration in the CNS, lung, and vascular endothelium.

However, postponing injection for 48 hours resulted in a significant fall in survival rate to 40% [27].

Inhaled fusion-inhibitory lipopeptides: One advantage of inhaled delivery is that it delivers the drug directly to the respiratory system, so efficiently addressing the principal viral entry mechanism. *In vivo* studies in Golden Hamster and African Green Monkey models revealed a 33% reduction in relative mortality risk for the African Green Monkey model [12,28]. Nanoparticle formulation is a promising future therapeutic approach; however, no *in vivo* or *in vitro* investigations have yet been conducted [29].

3.2 Vaccination

The investigation of various viral vectors, such as the vesicular stomatitis virus glycoprotein (VSV-G), canarypox virus, and rhabdovirus, has been carried out in the context of experimental vaccine development. In addition, a vaccine utilizing a recombinant measles virus (rMV) has exhibited encouraging results in terms of its potential for application in human subjects. According to a study conducted using a hamster model, it was observed that vaccination with recombinant VSV vectors exhibited notable efficacy [30].

Subunit vaccines: It has been shown that using highly specific epitopes or viral peptides is a realistic and cost-effective way to vaccine manufacturing. Bioinformatics tools suggest that the major epitopes capable of inducing an adequate immune response are certain sections of the F and G glycoproteins. These epitopes are thought to be excellent candidates for further exploration [31]. Research on African Green Monkey models has had a positive impact on the creation of a subunit vaccine generated from the oligomeric soluble form of G recombinant HeV glycoprotein. These studies demonstrated that this vaccination gives full protection against NiV and produces significant levels of IgG antibodies. The heightened immunogenicity and extraordinary efficacy reported in this trial give compelling support for the necessity for additional evaluation and, potentially, approval of the use of this medication in humans in the future [32,33].

Vector vaccines: *In vivo* investigations on pig and Golden Hamster animal models have yielded promising results using an attenuated virus expressing recombinant G/F NiV glycoproteins. These trials have effectively induced adequate serological responses using various viral vectors such as canarypox virus, vesicular stomatitis virus, and Venezuelan equine encephalitis virus. Furthermore, in experimental models using Golden Hamsters, virus-like particles derived from mammalian cells capable of expressing the F, G, and M viral proteins have been shown to elicit a strong neutralizing response and provide full protection against lethal doses of NiV [33].

mRNA-1215 vaccine: The National Institute of Allergy and Infectious Diseases (NIAID) and Moderna, a biotechnology company, have formed a partnership to accelerate the development of a potential messenger RNA (mRNA) vaccine. This vaccine is currently in Phase 1 of clinical trials, where its safety and immunogenicity are being studied. The vaccine under research contains genetic information for the F protein's prefusion state. This F protein is chemically linked to the G protein monomer (pre-F/G) seen in the Malaysian strain of Nipah virus (NiV) [34].

Passive immunization: a polyclonal serum against the G and F proteins remains a viable option for this purpose [33].

3.3 Prevention

3.3.1 Early outbreak detection and containment

Populational surveillance systems: In India and Bangladesh, various strategies have been used, including Nipah belt-focused hospital surveillance combined with increased efforts during the Nipah season, the establishment of a 24-hour hotline for reporting adverse health events, and the monitoring of mass media information [9, 35]. From 2007 to 2012, mass media monitoring was carried out by the National Media-Based Public Surveillance System, which proved to be a very effective, cost-efficient, and long-term technique of outbreak identification. This technique is especially appropriate for low-income countries with inadequate health infrastructure, such as Bangladesh, because it entails comprehensive monitoring of major media sources to quickly identify and analyze potential NiV outbreaks [9,36].

Exposure-based screening: In Bangladesh, from 2012 to 2013, the use of simple hospital admission questionnaires proved outstanding effectiveness and efficiency in early detection of

NiV-encephalitis cases and prevention of interhuman transmission. Inquiring about sap consumption and history of contact with febrile patients exhibiting altered cognition within the previous 30 days since symptom onset proved to be a valuable NiV screening tool, especially during Nipah season (with a recorded negative predictive value of 99% during wintertime). Furthermore, the use of screening questionnaires allows for a more efficient allocation of resources for NiV transmission prevention in hospital settings, where resources are frequently constrained [36].

3.3.2 Human transmission prevention

According to the Bangladeshi government, it is strongly advised to refrain from consuming raw date palm sap during periods of outbreaks, unless certain precautions have been taken. These precautions include the use of bamboo skirts to protect the sap during collection, or alternatively, boiling the sap for a duration of 10 minutes [37].

Populational/community educational intervention: Adapting a multilevel information campaign to address specific risk factors within specific populations, such as discouraging fresh sap consumption in rural areas and reducing direct contact transmission in hospital settings, improves the efficacy of educational efforts to prevent infectious diseases [9]. In 2009, significant messaging was distributed in rural areas of Bangladesh to discourage sap usage. The "only safe sap" campaign was the most effective technique, significantly raising illness comprehension and transmission knowledge. This message takes a harm-reduction approach, emphasizing abstinence as the best outcome while offering alternatives that reduce risk [38].

Physical barrier measures to prevent bat-to-human transmission: During the date palm sap harvesting season, which coincides with the Nipah outbreak time in Bangladesh, the eating of contaminated sap is the primary route for the development of Nipah virus (NiV) [39]. Local harvesters, called as "gachhis," collect and sell fresh sap early in the morning, and customers frequently consume it that same day. Unfortunately, in such cases, there is no decrease in viable virus load in contaminated sap, emphasizing the critical need for measures to prevent sap contamination from Pteropus spp., the reservoir of NiV [39].

Historically, gachhis, or experienced sap collectors, used a variety of ways to prevent sap against degeneration caused by the presence of bat urine and dung. The strategies used in this study include using tree branches as a protective barrier for the sap circulation area, applying lime to cure the bark, and installing bamboo skirts. Infrared cameras have provided solid evidence that bamboo skirts, generally known as "banas" in the local context, are the only effective method for preventing direct contact between bats and sap flow [40]. Camera footage shows that Pteropus spp. commonly visit date palm palms. This behavior has been shown to cause sap contamination by direct touch and feeding [40]. Further investigation is required to ascertain the scalability of the bana technique; nevertheless, its potential as a preventive tool continues to show great prospective. The implementation of measures aimed at restricting zoonotic transmission is widely acknowledged as the most efficacious and financially viable approach to controlling outbreaks in human populations. Moreover, this intervention stands out due to its affordability and simplified implementation, rendering it highly accessible to individuals belonging to the gachhi community [41,42]. Moreover, it is worth noting that this intervention aligns with the long-standing tradition of collecting and consuming recently extracted sap, thereby ensuring the preservation of this important cultural heritage [43].

4. FUTURE DIRECTION

Enhanced Surveillance and Diagnostic Capabilities: We advocate for strengthening surveillance systems to swiftly identify and respond to outbreaks of the Nipah virus. Integrating modern genomic technologies and bioinformatics into existing public health infrastructure is crucial. This enhancement will enable more precise monitoring and faster containment efforts, helping to prevent the spread of the virus before it reaches critical levels [44]. **Advancements in Treatment Options:** We emphasize the need for continued collaboration to advance clinical trials for promising treatments. International partnerships are essential in this regard, as they can help accelerate the development and availability of effective treatments. These efforts ensure that new therapies meet rigorous safety standards and are adaptable to diverse healthcare environments around the world [45]. **Progress in Vaccine Research and Accessibility:** The development of effective vaccinations remains a

top goal. The positive results of vaccine trials, such as those for the mRNA-1215 vaccine, are encouraging [45]. However, we must address the challenges that come with moving from successful clinical trials to a more general application. Improving production capabilities and ensuring equitable distribution are key to making these vaccines available, especially in countries most prone to outbreaks.

Community Engagement and Preventive Education: We also recognize the critical role of community engagement in prevention strategies. Extensive educational programs that inform at-risk populations about preventive measures are vital. These programs should be culturally sensitive and leverage local practices to effectively reduce transmission risks. For instance, promoting safer practices such as avoiding the consumption of raw date palm sap in endemic areas can significantly mitigate the risk of human transmission. **Adopting a One Health Approach:** We also recommend adopting a One Health approach that considers the interconnected health of humans, animals, and the environment. This holistic strategy encourages a multidisciplinary response to health threats and promotes sustainable practices that can help prevent future outbreaks [41]. We believe that by addressing these key areas, we aim to enhance global cooperation and focus on integrated health interventions and moreover these efforts are crucial for better managing the Nipah virus and ultimately reducing its threat to global health, ensuring the safety and well-being of communities worldwide.

5. PROBABLE SOLUTION

Improved Early Detection Systems: We emphasize the need to implement better early detection systems. Using cutting-edge surveillance technologies, NiV cases can be identified more quickly. Once cases are recognized, rapid response measures are critical for preventing widespread transmission and efficiently managing outbreaks. Investing in these technologies and training healthcare staff on how to utilize them will give us an important tool in the fight against NiV. **Therapeutic Development and Accessibility:** We must speed up therapeutic development and availability. Extending research into antiviral drugs and monoclonal antibodies that have showed success in preclinical trials is extremely important. Furthermore, establishing mechanisms for emergency use authorization and faster review processes during outbreaks would guarantee that these treatments reach individuals in need swiftly and efficiently.

Vaccine Research and Implementation: The advancement of vaccine research and implementation is a top goal. As potential vaccines go through clinical trials, collaborations with governments and international health organizations will be critical to the implementation of vaccination programs. Addressing logistical issues in vaccine distribution also guarantees that populations, particularly those in poor geographical areas, have enough access to preventive measures**. Community-Based Prevention strategies:** We support the use of community-based prevention strategies. These should involve educational outreach to communities about the risks of NiV and the behaviors which increase the likelihood of transmission. Programs focusing on behavioral change are critical, especially in areas where cultural traditions contribute to virus propagation. **Integration of One Health Strategies:** Implementing One Health solutions that cover human, animal, and environmental health is critical. Collaboration across sectors can result in more effective NiV monitoring, control, and prevention. Establishing frequent communication channels and collaborative reaction mechanisms would assist manage NiV risks more completely and prevent the virus from spreading from animal hosts to humans. By focusing on these solutions, we want to build a strong foundation for managing NiV. The effective application of these methods will not only control current outbreaks but also improve preparedness for future health issues, thereby ensuring global health security [46].

6. CONCLUSION

Over the past few years, there has been significant progress in addressing the Nipah virus (NiV), a concerning zoonotic disease that poses serious risks to global health. After conducting an extensive review, we have discovered some exciting advancements in antiviral therapies and vaccine research. However, it is important to note that there are still significant challenges to overcome before these findings can be practically implemented. Various drugs, including Ribavirin and Remdesivir, have shown effectiveness in research and development. However, their effectiveness can vary significantly in different studies, emphasizing the importance of conducting more clinical trials.

Moreover, the utilization of monoclonal antibodies such as m102.4 presents a potent tool for post-exposure treatment, demonstrating considerable potential in preclinical settings. Regarding the vaccine progress, there have been potential advancements in early clinical trials, particularly with the use of mRNA vaccines. These new technologies have the potential to be quickly deployed during outbreaks, which is a significant development. Although there have been significant advancements, it remains essential to further improve surveillance systems and public health infrastructures on a global scale to effectively manage and prevent outbreaks. It is therefore essential to prioritize educational initiatives in at-risk areas to effectively reduce the spread of diseases by promoting behavioral changes, specifically addressing practices such as the consumption of raw date palm sap. In the future, we will need to stimulate global collaboration and ensure equitable dissemination of these technological developments in medicine. Adopting a One Health approach that combines human, animal, and environmental health efforts can help us better manage NiV and other zoonotic illnesses. Furthermore, continuous investment in research and development, as well as proactive public health policies, will be extremely important in mitigating the impacts of this deadly NiH virus.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DECLARATIONS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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