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Review

Glycoprotein G-Based Vaccines for Nipah Virus: Epidemiology, Molecular Insights, Benefits, and Limitations

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Abstract: Nipah virus (NiV) is a highly virulent zoonotic pathogen associated with significant mortality rates and limited treatment options, posing a significant public health threat. This review explores the epidemiology, molecular structure, and vaccine development efforts targeting glycoprotein G, a critical component of the virus's entry mechanism. Advances in structural biology and immunogenetics have highlighted the potential of glycoprotein G-based vaccines in preventing NiV infections. Despite promising preclinical results, challenges such as immune evasion, safety concerns, and limited clinical trials persist. Additionally, we examine the benefits of glycoprotein G-based vaccines in enhancing immune responses and preventing viral entry, as well as the limitations posed by genetic diversity and cross-reactivity. This review highlights the critical need for ongoing research to overcome existing challenges and guide future vaccine development efforts against NiV. It further underscores the necessity of innovative approaches in vaccine design to reduce the global burden of NiV infections. Glycoprotein G-based vaccines represent a promising avenue for combating NiV infections. Advances in structural biology, immune system targeting, and delivery system technology are paving the way for more effective vaccines. However, overcoming challenges such as cross-reactivity and safety concerns will require continued innovation and collaboration.

Keywords: Nipah Virus; Outbreak; Vaccine Development; Immunogenetics; Glycoprotein G

1. Introduction

Emerging and re-emerging viral pathogens pose a significant threat to global health, a reality underscored by multiple outbreaks across the globe in the past few decades. Among such pathogens is the Nipah virus (NiV), a zoonotic virus that was first identified in 1998–1999 when outbreaks occurred in Malaysia and Singapore, leading to considerable morbidity and mortality [1,2]. Since then, the virus has garnered increasing attention due to its potential for rapid spread, high case-fatality rates, and lack of definitive treatment or vaccine. NiV belongs to the genus *Henipavirus* under the family *Paramyxoviridae*, which also includes Hendra virus (HeV). Bats, particularly

those of the genus *Pteropus*, have been identified as the reservoir hosts for NiV, harboring the virus in their saliva and urine without manifesting severe disease symptoms [3]. Transmission to humans often occurs through direct exposure to infected animals or consumption of food products contaminated by infected bats, such as raw date palm sap. Additionally, person-to-person transmission has been documented in certain outbreaks, raising alarms about the virus's epidemic potential [1,4].

One of the critical challenges posed by NiV is its variable incubation period. While early symptoms typically manifest within a few days to two weeks post-exposure, there are documented cases where the incubation period stretched to as long as 45 days [2]. During this extended incubation phase, infected individuals may not exhibit overt clinical signs. Yet, they can potentially transmit the virus to others, compounding the difficulty of implementing timely public health interventions. Indeed, epidemiological reports highlight that NiV infection can be highly contagious among pigs even before overt clinical symptoms appear, thus complicating containment strategies in farm settings [3]. The clinical manifestations of NiV infection can be severe: initial symptoms include fever, headache, and respiratory distress, but the disease may rapidly progress to encephalitis, seizures, and coma within 24 to 48 hours [4]. Such rapid clinical deterioration, coupled with case-fatality rates ranging between 40% and 75%, emphasizes the need for effective preventive measures [5].

Beyond the acute phase of the infection, survivors often face long-term neurological sequelae, such as persistent seizures and behavioral changes, underscoring the importance of designing treatments and interventions that not only prevent fatality but also mitigate long-term complications [6]. Although bats are considered the primary natural reservoir for NiV, direct contact between humans and bats is relatively uncommon, leading researchers to postulate that intermediate hosts frequently facilitate spillover events. Early outbreaks strongly implicated pigs as an intermediate host, while other studies have suggested that camels could also harbor NiV, serving as a possible zoonotic source [7].

Despite the clear and pressing threat NiV poses, no antiviral drugs or vaccines have received regulatory approval for either prophylaxis or treatment. Current patient management strategies rely predominantly on supportive care, addressing complications such as respiratory distress or managing seizures as they arise [8]. However, research efforts have intensified in recent years. Several experimental approaches—including immunotherapy with monoclonal antibodies—are undergoing early clinical investigations [9]. Moreover, drugs like remdesivir, previously employed against diseases such as Ebola virus infection, have shown promise in non-human primate models when administered soon after NiV exposure [9]. Of particular interest is the partially protective effect of a Hendra virus vaccine, originally approved for use in horses, which has also demonstrated cross-protection against NiV in certain experimental setups [10]. Parallel efforts focus on developing targeted NiV vaccines, and multiple preclinical studies have highlighted glycoprotein G (NiV-G) as an especially promising immunogen [11,12]. This glycoprotein is crucial for viral attachment and subsequent entry into host cells, functioning in synergy with the fusion protein to facilitate membrane fusion. Consequently, NiV-G is a prime target for the induction of virus-neutralizing antibodies.

The significance of NiV-G in the virus's lifecycle has driven a surge in bioinformatics-led vaccine design initiatives. Bioinformatics tools enable the identification of immunogenic epitopes with the potential to elicit robust humoral and cellular immune responses in vivo [13,14]. These computational platforms allow for the rapid screening of epitope candidates from large viral protein datasets, facilitating the design of recombinant vaccine constructs that can be tested in animal models. By integrating structural insights—such as those gleaned from cryo-electron microscopy—researchers aim to understand how NiV-G interacts with neutralizing antibodies and how these interactions can be optimized in a vaccine formulation [15]. Furthermore, structural elucidation of NiV-G supports the rational design of therapeutics that either block receptor binding or prevent conformational changes necessary for fusion.

A notable breakthrough in structural research on NiV-G was provided by Wang et al. [15], who used cryo-electron microscopy to map the complete tetrameric structure of this glycoprotein. Their findings built upon earlier work that had only characterized the head domain of NiV-G. Through these advanced imaging techniques, they identified binding sites for two distinct monoclonal antibodies on opposite sides of the NiV-G head domain. Interestingly, the antibodies appeared to work synergistically, obstructing different functional aspects of NiV-G and minimizing the likelihood of viral escape mutants. This concept of employing antibody combinations that bind to spatially distinct epitopes could inform future vaccine design, where multi-epitope targets may reduce the probability of immune evasion.

In parallel, epidemiological data reinforce the urgency of these vaccine development efforts. NiV outbreaks have not been limited to Malaysia and Singapore; Bangladesh and parts of India have also experienced repeated episodes of NiV infection since 2001 [5,16]. The geographical spread of NiV has even been detected beyond South and Southeast Asia, with serological evidence of Henipavirus circulation reported in regions of Africa and the South Pacific [17]. The global distribution of *Pteropus* bats further suggests the potential for NiV to emerge in new locales, fueling concerns of a possible pandemic. Moreover, variations in viral strains—such as the differences between the Malaysia (NiV-M) and Bangladesh (NiV-B) strains—highlight the need for broadly protective vaccine constructs capable of addressing strain-specific pathogenicity traits [18,19].

The high case-fatality rate and the neurotropic nature of NiV amplify the importance of ensuring that any vaccine candidate undergoes rigorous safety assessment. Several technological platforms have been explored, including subunit vaccines, vector-based vaccines, virus-like particles (VLPs), DNA vaccines, and mRNA-based approaches [8, 9, 20]. Each platform presents unique advantages and potential drawbacks. For instance, subunit vaccines allow for the targeted delivery of immunogenic proteins, minimizing the risks associated with live-attenuated pathogens. Meanwhile, viral vector platforms have demonstrated robust immunogenicity in preclinical models but may be hindered by pre-existing immunity to the vector in some human populations. VLPs mimic the morphological properties of viruses without harboring infectious genetic material, offering a balance between immunogenicity and safety. Similarly, mRNA vaccines have risen to prominence for their adaptability and relatively speedy manufacturing processes, though they require specific considerations regarding storage and distribution.

In recent years, there has also been progress in improving vaccine adjuvants and delivery systems. Nanoparticle-based carriers, for example, can enhance the stability of antigenic epitopes and facilitate controlled antigen release, thereby improving the magnitude and duration of immune responses [21,22]. These systems can be customized to deliver multiple antigens or adjuvants simultaneously, potentially eliciting broader and more robust immunity. Additionally, adjuvants that activate pattern recognition receptors (e.g., Toll-like receptors) can help shape a more potent immune response. For NiV, the use of such advanced platforms could translate into vaccine candidates that not only elicit neutralizing antibodies against NiV-G but also induce cytotoxic T lymphocyte (CTL) responses that help clear infected cells.

Despite these promising developments, a fully licensed NiV vaccine is yet to emerge. Regulatory pathways for new vaccines typically involve multiple phases of clinical trials, which can be both time-consuming and resource-intensive. This underscores the need for continued international collaboration and sustained investment, as NiV remains a high-priority pathogen according to organizations like the World Health Organization (WHO) and the Coalition for Epidemic Preparedness Innovations (CEPI). In that context, the overarching aim of ongoing research is to develop an effective, safe, and globally accessible NiV vaccine that addresses diverse strains and offers durable protection. The overarching aim of this study is to critically synthesize and contextualize the most recent NiV research—particularly structural and immunological insights into glycoprotein G—while evaluating existing vaccine platforms (including subunit, vector-based, VLP, and mRNA approaches) and ultimately proposing a cohesive framework that leverages bioinformatics, structural biology, and immunological data to accelerate the clinical translation, regulatory approval, and global implementation of effective NiV vaccines.

2. The Epidemiological Patterns of Nipah Virus Infection

The initial outbreak of the Nipah virus was documented between 1998 and 1999 in Malaysia and Singapore [15]. Between September 1998 and June 1999, multiple individuals with a history of close contact with swine were diagnosed with severe viral encephalitis, suggesting direct zoonotic transmission of the virus from pigs to humans [16]. Between 1998 and 1999, a total of 246 cases of febrile encephalitis attributed to Nipah virus were reported in Singapore and Malaysia [17], with an estimated mortality rate of approximately 40% [18]. In 2001, a second outbreak of Nipah virus was documented in the Mehrpur district of Bangladesh and the city of Siliguri in West Bengal, India, occurring in geographically non-contiguous regions [19]. As of 2010, Bangladesh had recorded a total of nine Nipah virus outbreaks. An additional outbreak in 2011 resulted in 15 reported fatalities due to Nipah virus infection [20]. Epidemiological research has indicated that Nipah virus circulation across Asia, Africa, and the South Pacific has led to sporadic outbreaks, facilitated by both human-to-human and zoonotic transmission [21]. Over the past two decades, this disease has resulted in hundreds of fatalities and continues to pose a significant threat to both human populations

and domesticated animals. Recent outbreaks of NiV were also reported in Kerala, India, in May 2018 and June 2019, marking the first emergence of the virus in southern India [23]. NiV is classified into two distinct strains: the Malaysia strain and the Bangladesh strain, which exhibit 91.8% sequence homology [24]. The virus is associated with severe respiratory illness and encephalitis, demonstrating high case fatality rates (CFR) ranging from 40% to 75% [25].

3. Glycoproteins G and Vaccine Development Against Nipah Virus

The entry of the Nipah virus into host cells necessitates membrane fusion between the virus and the host cell. This process is facilitated by the virus's internal mechanisms, specifically its binding and fusion glycoproteins (**Figure 1**). These factors likely work together to initiate viral fusion to the host cell [22]. Wang et al. [23] employed cryo-electron microscopy (cryo-EM) to elucidate the complete tetrameric structure of the virus's glycoproteins. Previously, the researchers had mapped only one part of the protein, known as the head domain. Using this structural knowledge, the team determined where two previously discovered different antibodies bind to the adhesive glycoprotein. They found that the antibodies work synergistically to prevent the virus from entering cells by binding to opposite sides of the adhesive glycoprotein's head. The antibody combination reduced the emergence of escapee viral mutants, which evade detection by the immune system by making changes to where the antibodies bind. Recent molecular discoveries have offered novel insights into the mechanisms by which the Nipah virus invades host cells and the corresponding immune responses that mitigate viral infection. The findings suggest a multifaceted approach to both the prevention and treatment of these life-threatening diseases. While a vaccine has been approved for use in horses, an adapted version has progressed to human clinical trials [24].

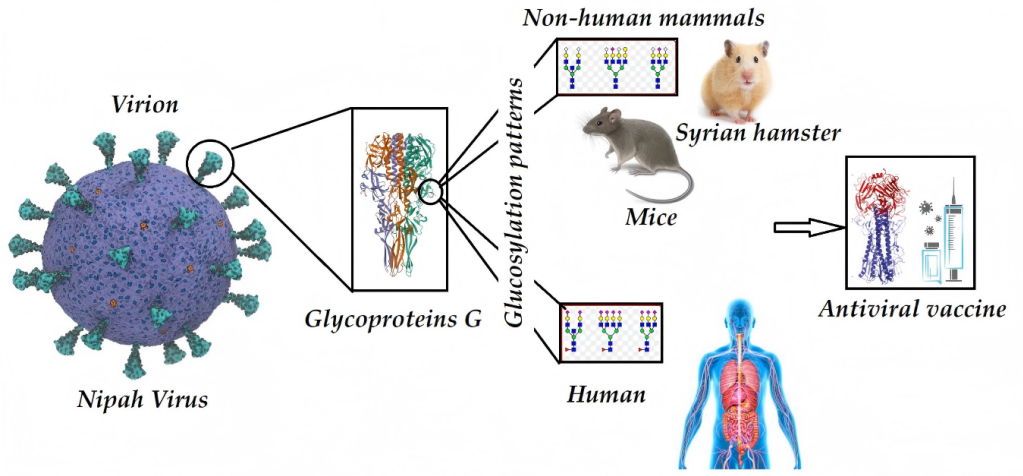

Figure 1. The illustration of roadmap from virion of Nipah to vaccine development using glycoprotein G.

Long-term surveillance of vaccine recipients is critical to assess safety and efficacy, particularly in neurologic adverse effects. Given NiV's propensity to cause severe encephalitis and long-term neurological sequelae, it is essential to monitor whether the vaccine itself induces any neuroinflammatory or neurologic complications. Additionally, surveillance should differentiate between adverse effects caused by the vaccine and those resulting from potential breakthrough infections, even if attenuated. Such monitoring will provide valuable insights into the vaccine's impact on neuroinflammatory states and its overall safety profile in humans [8,26].

4. Methods

This systematic review was conducted to synthesize the current understanding of NiV pathogenesis, NiV-G, and the progress in NiV-G-based vaccine development. A comprehensive search strategy was employed to identify relevant studies published up to February 2025. The PubMed, Scopus, and Web of Science databases were systematically searched using a combination of Medical Subject Headings (MeSH) terms and free-text keywords, such as "Nipah virus," "NiV-G," "Henipavirus," and "vaccine development," combined with Boolean operators (AND, OR)

to refine the results. Additionally, the reference lists of included articles were manually reviewed to identify any additional studies that met the inclusion criteria.

Studies were included if they were original research articles focusing on NiV pathogenesis, NiV-G analysis, or NiV-G-based vaccine development, utilizing either preclinical or clinical models, and providing sufficient detail for quality assessment. Conference abstracts, opinion pieces, and non-English publications without available translations were excluded.

Two independent reviewers screened the titles and abstracts of all identified studies for eligibility. Full texts of potentially relevant articles were then assessed for inclusion. Any disagreements between reviewers were resolved through discussion or consultation with a third reviewer. Data extraction was performed using a standardized form, capturing study characteristics (e.g., author, year, country), vaccine platforms, experimental models, key outcomes, and study limitations.

The quality of included studies was assessed using a modified quality appraisal checklist, and the strength of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. A qualitative synthesis of the findings was conducted to summarize the current knowledge on NiV pathogenicity, NiV-G immunobiology, and vaccine immunogenicity. While a quantitative meta-analysis was considered, the heterogeneity in study designs and outcomes often precluded the pooling of data.

Since the first appearance of Nipah, several attempts have been conducted to identify promising vaccine candidates against this virus using surface glycoproteins, especially glycoprotein G, of which each reported some limitations (**Table 1**).

Table 1. The available literature on the effects of glycoproteins G vaccine against Nipah virus and their limitations.

Study ID	Study Type	Sample	Intervention	Findings	Limitations
Moon et al., 2024 [25]	Animal model	Six-week-old male BALB/c randomly were randomly assigned to eighteen experimental groups (n = 8 per group)	NiV-F/G Vaccine	Positive immunogenic vaccine	Protective effects is yet to be elucidated live virus challenges
Watanabe et al., 2023 [26]	Animal model	Female 4–5-week-old Syrian golden hamsters	NiV- F/G Vaccine	Successfully prevent lethal infection	Maintains proliferative activity in certain cultured cells, including renal cell lines
Lu et al., 2023 [27]	Animal model	BALB/c mice (6–8 weeks old, female) and Syrian hamsters (5–6 weeks old, female)	NiV DNA vaccine (DNA-G)	A significant decrease in the viral load	No or minimal detectable levels of infectious particles were observed in the lungs, brain, and spleen
Medina-Magües et al., 2023 [28]	Animal model	BALB/c and AJ mice (4-week-old mixed sex)	NiV- F/G Vaccine	A promising vaccine candidates	Limitation in the route of admiration
de Wit et al., 2023 [29]	Animal model	Adult African green monkeys; 3–6.5 kg (n = 20)	NiV- F/G Vaccine	Induced high neutralising antibody titers	Unable to incorporate a recently isolated virus strain from India
Monath et al., 2022 [30]	Animal model	Outbred ICR mice and Golden hamsters (*Mesocricetus auratus*)	NiV- F/G Vaccine	have a clinically acceptable safety profile for human use	The risk of replication in extra-neural tissues
Dang et al., 2021 [31]	Animal model	Outbred mice	NiV- F/G Vaccine	Neutralizing NiV	-
Loomis et al., 2020 [32]	Animal model	10 CB6F1/J mice	NiV- F/G Vaccine	Elicit neutralizing activity	Instrument limitations prevented analysis above 80°C
Li et al., 2020 [33]	Animal model	BALB/c mice (6–8 weeks, female)	NiV- F/G Vaccine	Induced a strong antibody response	An antibody response with restricted cross-reactivity
Shuai et al., 2020 [34]	Animal model	mice and pigs	NiV- F/G Vaccine	Significant NiV neutralizing antibody	The risk of replication in extra-neural tissues

Table 1. *Cont.*

Study ID	Study Type	Sample	Intervention	Findings	Limitations
Kalodimou et al., 2019 [35]	Animal model	IFNAR and C57BL/6 mice	NiV- F/G Vaccine	Activated cellular immune responses	Limited insights into NiV-specific T-cell immune responses
Nie et al., 2019 [36]	Animal model	Hartley guinea pigs (females, 200 g weight) and Balb/c mice (females, 15 g weight)	NiV- F/G Vaccine	Provide sufficient protection	No statistically significant variation was observed in the ED50
Johnston et al., 2017 [37]	Cell line model	HEK293T (ATCC) cells	NiV- F/G Vaccine	Improve our understanding of the viral assembly	-
van den Pol et al., 2017 [38]	Animal model	18 mice	NiV- F/G Vaccine	Provide sufficient protection	limitation in clinical use due to its neurotropic effect
Pallister et al., 2011 [39]	Animal model	Eight male ferrets aged 12–18 months	NiV- F/G Vaccine	Provide sufficient protection	-
Wang et al., 2006 [40]	Animal model	10–12 week old female BALB/c mice	NiV- F/G Vaccine	could be safe subunit vaccines	-

Note: NiV: Nipah virus.

5. Discussion

The evolving literature on NiV has solidified its status as a high-priority zoonotic pathogen with recognized potential to trigger outbreaks of considerable scale. Initial recognition of NiV's threat stemmed from dramatic outbreaks in Malaysia and Singapore in the late 1990s, events that prompted broad-based investigations into the virus's biology, its reservoir hosts, and modes of transmission [27–32]. Since then, sporadic yet severe outbreaks in Bangladesh and India have underscored NiV's capacity for causing respiratory distress, encephalitis, and long-term neurological complications in survivors. The virus's classification within the Henipavirus genus ties it closely to HeV, another lethal zoonotic pathogen. While Hendra has caused outbreaks primarily in horses and humans in Australia, NiV continues to be associated with a broad spectrum of hosts, including swine, bats, and humans [28,29].

Beyond the documented outbreaks, NiV's capacity for person-to-person transmission and its extensive host range underscore the possibility of a larger epidemic or even a pandemic if containment strategies falter [29,30]. In various outbreak settings, case-fatality rates have ranged from 40% to over 70%, with some localized incidents in Bangladesh and India showing extreme mortality [31]. Such high lethality elevates NiV to a top-tier concern on the global pathogen watchlist, aligning with its status as a priority pathogen for accelerated vaccine and therapeutic development by organizations like the WHO [27,28]. Coupled with neurological sequelae in many survivors, these outcomes demand interventions that go beyond merely reducing acute mortality, aiming instead to mitigate the long-term neurological and psychiatric morbidities that plague individuals recovering from NiV infection [32].

6. Pathogenesis and Immune Response

NiV pathogenesis is intimately linked to its tropism for vascular endothelial cells and neuronal tissues [33]. This dual tropism aligns with the distribution of the ephrin-B2 and ephrin-B3 receptors—molecules exploited by NiV for cell entry. The virus's two surface glycoproteins, NiV-G and the fusion glycoprotein (F), operate in tandem to initiate infection: NiV-G binds to host cell receptors, while NiV-F executes the membrane fusion needed for viral genome entry into the cytoplasm [33]. Post-fusion, NiV can disseminate systematically, infecting multiple organ systems and often culminating in severe encephalitic or respiratory forms of the disease [30,31].

In parallel, the host immune response to NiV can be quite robust, featuring both innate and adaptive components. Early innate immunity relies on interferon signaling pathways, natural killer (NK) cells, and macrophages to control viremia [34,35]. However, NiV has evolved multiple strategies to evade or inhibit host antiviral responses, including the suppression of interferon production and signaling through viral proteins that interact with critical nodes of the innate immune system [33]. A decisive factor in determining clinical outcome appears to be the bal-

ance between early viral replication and the ability of the immune response to curb viral spread before irreversible neuronal or pulmonary damage occurs [28,35].

7. Role of Glycoprotein G in Immune Defense

Among the structural components of NiV, NiV-G is especially prominent both for its mechanistic importance and its utility as an immunological target [36,37]. NiV-G's head domain mediates binding to ephrin-B2/B3, while its stalk domain contributes to stabilizing the overall conformation. Cryo-electron microscopy (cryo-EM) studies have clarified that NiV-G forms a tetrameric assembly, with the potential for multiple monoclonal antibodies (mAbs) to bind to different epitopes simultaneously [36]. This observation highlights a strategic advantage: polyclonal or combination antibody therapies that target multiple sites can maximize neutralization and reduce the likelihood of escape mutants. Furthermore, antibodies directed against NiV-G may also engage in antibody-dependent cellular cytotoxicity (ADCC), thus recruiting effector cells to clear infected targets [35,37].

Historically, a substantial body of research on NiV-G's immunological role has focused on generating neutralizing antibodies capable of blocking the receptor-binding pocket. This interference can effectively halt membrane fusion by preventing NiV-F from assuming the conformations required for viral penetration [36]. The capacity of NiV-G to induce potent neutralizing responses has thus propelled efforts to develop subunit vaccines, viral vector-based constructs expressing NiV-G, and VLPs that incorporate NiV-G and F in their native conformation.

8. Epidemiological Considerations: The Need for Vaccines

Despite relatively contained outbreaks in Malaysia, Singapore, Bangladesh, and India, NiV's versatility in jumping from bats (its primary reservoir) to other species raises concern for expansions into new geographic areas, particularly as Pteropus bat species inhabit large swaths of Africa, Asia, and Oceania [28,29,33]. Transmission events often begin with direct contact with infected animals—pigs in Malaysia, for instance—yet human-to-human transmission has also been documented, especially in Bangladesh [31]. Additionally, anecdotal reports exist of NiV presence in raw date palm sap, which bat excreta can contaminate. Consumption of this sap has been implicated as a direct route of NiV transmission to humans [29,33].

A salient complication is NiV's extended incubation period, which can exceed a month in some cases [28]. Individuals in a prolonged incubation phase remain asymptomatic, evading detection while potentially shedding virus. Such "stealth transmission" underscores the need for robust vaccination strategies, whether as routine prophylaxis in high-risk regions or as post-exposure interventions during outbreak scenarios [2,3]. Given that the virus tends to cause a swift progression to encephalitis and respiratory compromise once symptoms manifest, effective immunization could dramatically reduce the burden on healthcare systems and improve patient outcomes.

9. Vaccine Platforms

Subunit vaccines against NiV often rely on purified NiV-G—either full-length or domain-specific fragments—combined with potent adjuvants [30]. This approach offers strong safety advantages because it avoids introducing whole viruses (whether live-attenuated or inactivated). The immunogenic head domain of NiV-G, containing key neutralizing epitopes, is typically the focal point [36]. However, one of the main constraints is generating a balanced immune response that not only stimulates high titers of neutralizing antibodies but also activates T cells effectively. Traditionally, subunit vaccines have been considered more adept at provoking B-cell (humoral) immunity than cellular immunity [30,38]. As NiV infection quickly infiltrates tissues and cells, a robust T-cell response—particularly cytotoxic T lymphocytes (CTLs)—may be essential for clearing intracellular virus.

Adjuvant choice and formulation significantly impact the effectiveness of NiV-G subunit vaccines [27,32]. For instance, nanoparticle-based adjuvants that incorporate Toll-like receptor agonists have shown promise in preclinical models by bolstering both antibody and T-cell responses [38]. One crucial hurdle lies in ensuring that the chosen subunit fragments retain the same conformation found in native NiV-G, because misfolded or improperly presented antigens can diminish immunogenicity [36]. Structural biology inputs—supported by cryo-EM data—help guide the engineering of subunit vaccines that most closely mimic the functional epitopes on NiV-G.

Vector-based platforms deploy replication-deficient or attenuated viruses—such as adenovirus (Ad), vesicular stomatitis virus (VSV), or measles virus (MeV)—to express NiV-G in vivo [39,40]. These vectors typically induce

robust immune responses, partly because viral gene expression in host cells leads to the presentation of antigenic peptides on both MHC class I and II pathways [31,32]. Consequently, a balanced humoral and cellular immune response can be elicited. Indeed, some adenovirus-based NiV-G vaccines have shown near-complete protection against lethal challenge in hamster and ferret models [41,42].

Nevertheless, several challenges persist. Pre-existing immunity to commonly used vectors like human adenovirus can reduce vaccine efficacy, as neutralizing antibodies against the vector itself may degrade or clear it before adequate NiV-G expression occurs [35]. Alternative vectors—for instance, simian adenoviruses (ChAd) or non-human paramyxovirus backbones—aim to circumvent this issue [39]. Additionally, regulatory scrutiny of vector-based vaccines is meticulous, especially given NiV's marked neurotropism. Even a small theoretical risk of vector reversion or neuropathic side effects warrants extensive safety evaluations [28].

10. Virus-Like Particles

VLPs mimic the surface glycoprotein arrangement of the native virus without harboring genetic material [28,29]. In NiV's case, VLPs can be engineered to incorporate G and F proteins in an authentic spatial configuration, promoting the induction of neutralizing antibodies that recognize native conformational epitopes. VLP-based vaccines for paramyxoviruses, including NiV, have demonstrated strong immunogenicity and protective efficacy in small animal models [39,40]. However, large-scale production requires sophisticated bioprocessing to ensure consistent particle assembly, proper glycoprotein display, and purity [28].

One advantage of VLPs is their capacity to present multiple viral antigens simultaneously, which could broaden the protective response beyond NiV-G. The inclusion of NiV-F or matrix proteins may enhance T-cell immunity [36]. Achieving such a multivalent display within a single VLP construct can potentiate synergy between humoral and cellular arms. Nonetheless, cost and manufacturing complexities remain areas of active investigation, particularly if VLP platforms are to be deployed in resource-limited settings with minimal cold-chain infrastructure [29].

11. Nucleic Acid Vaccines (DNA and mRNA)

Fueled by the success of mRNA vaccines in recent pandemic responses (particularly against SARS-CoV-2), nucleic acid platforms have drawn considerable attention for NiV [3,24,43]. DNA vaccines encoding NiV-G have been shown to induce durable humoral and cell-mediated responses in animal models, although vaccine efficacy can hinge on delivery methods such as electroporation [27,30,42]. Meanwhile, mRNA-based vaccines exploit in vivo transcription to produce NiV-G, prompting robust antigen-specific immune responses [38]. Some studies have noted that mRNA formulations, when encapsulated in lipid nanoparticles, can elicit higher antibody titers than comparable DNA constructs, although inter-study variances are significant [43].

The major advantages of nucleic acid vaccines include the speed of design and ease of iterative antigen updates if new NiV strains or variants emerge [34]. This modularity could be pivotal for a rapidly evolving pathogen. However, distribution hurdles—particularly the need for ultra-cold storage for certain mRNA formulations—and the cost of manufacturing at scale remain hurdles in low-resource settings [37]. Moreover, as with any novel platform, long-term safety data in large, diverse populations are still accumulating.

12. Immune Evasion and Strain Variability

Despite extensive progress, NiV maintains an impressive capacity for immune evasion, a point underscored by structural data showing how subtle changes in NiV-G's receptor-binding pockets might reduce antibody affinity [36]. Viral evolutionary pressures may select for variants that diminish the efficacy of certain neutralizing antibodies, thereby complicating vaccine development. One strategy to thwart immune escape is the design of polyvalent or multi-epitope vaccines that induce antibodies against multiple distinct epitopes on NiV-G. This approach, however, increases manufacturing complexity and may demand advanced structural biology tools—such as cryo-EM combined with site-directed mutagenesis—to map epitope redundancy and synergy accurately [28,36].

Additionally, geographic variants of NiV—particularly the Malaysian strain (NiV-M) and the Bangladesh strain (NiV-B)—have demonstrated differences in pathogenicity and transmissibility. NiV-B is often associated with more frequent person-to-person transmission and a higher case-fatality rate [39,40]. Although some NiV-G-based vaccine candidates exhibit cross-neutralizing activity against both strains, the extent of this cross-reactivity can vary. A

universal NiV vaccine would ideally incorporate conserved antigenic regions from multiple strains, minimizing the risk of a strain-specific vaccine failing in an outbreak scenario dominated by a different variant [31,33].

13. Regulatory Challenges and the Clinical Trial Landscape

Vaccine licensure for NiV is inherently complicated by the sporadic nature of outbreaks [29, 30]. Conducting Phase III efficacy trials often requires a sufficiently high incidence of natural infection to demonstrate a clear protective effect, a logistical challenge in regions where outbreaks are unpredictable. In response, the scientific community is exploring adaptive trial designs and employing "animal rule" pathways in some jurisdictions. Under the U.S. Food and Drug Administration's (FDA) Animal Rule, for instance, efficacy data from well-validated animal models can support licensure when human trials are ethically or logistically infeasible [28,32]. Nonetheless, confirmatory human immunogenicity and safety data remain critical, highlighting the necessity for strong international collaboration between affected countries and global health agencies.

Moreover, the potential neurotropism of NiV raises the bar for vaccine safety [30]. Vaccine candidates must be rigorously vetted to ensure they do not exacerbate neurological conditions or trigger autoimmune responses in the central nervous system. This requirement extends the typical timelines for preclinical toxicology and Phase I/II trials, which must incorporate detailed neurological assessments [3,33]. Managing public perceptions around safety is also paramount, as any adverse events—real or perceived—could hamper vaccine uptake in vulnerable regions.

14. Long-Term Protection and Correlates of Immunity

Relatively few longitudinal studies have probed immune persistence following NiV vaccination, leaving an important gap in understanding the durability of protection [27,30]. Animal models suggest that some vaccines can elicit protective immunity that lasts several months, but whether this extends to years remains uncertain [37]. Identifying validated correlates of protection (e.g., neutralizing antibody titer thresholds, functional T-cell responses) would greatly streamline both clinical development and post-licensure surveillance [34]. If well-defined immunological markers are established, future studies could rapidly gauge the relative efficacy of new or updated vaccines without waiting for a significant outbreak.

15. A "One Health" Perspective

NiV's zoonotic transmission cycle requires a multifaceted control strategy that integrates human, animal, and environmental interventions. Bats of the Pteropus genus serve as primary reservoirs, often shedding virus via saliva, urine, or feces. Intermediate hosts, such as pigs, amplify NiV and bring the virus into closer contact with humans [28,29]. Understanding the ecological and environmental drivers—such as deforestation, habitat fragmentation, and climate change—that increase human-bat interface is critical for preemptive measures. Vaccinating swine populations in endemic or at-risk regions could also reduce spillover events to farm workers [28,34].

From a broader vantage point, NiV vaccine research exemplifies the concept of "One Health," wherein health outcomes in humans are closely tied to animal and environmental health. Surveillance systems that track bat colonies for NiV presence, along with efforts to educate communities about avoiding raw date palm sap or direct contact with potentially infected animals, are vital to a comprehensive control strategy [31, 33]. An effective NiV vaccine—whether for human or veterinary use—would be a central pillar in this integrated framework.

16. Lessons from Other Emerging Pathogens

The urgency surrounding NiV vaccine development is reminiscent of recent outbreaks involving Ebola virus, Zika virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Each episode has demonstrated that swift, large-scale vaccine trials can be executed when propelled by global partnerships and sufficient funding [29,30,38]. The success of mRNA and viral vector platforms in COVID-19 suggests that NiV vaccine candidates using analogous technologies may be fast-tracked if robust preclinical data are in place [27, 37, 43]. Moreover, knowledge transfer in areas such as large-scale manufacturing, distribution logistics, and public communication can expedite the NiV vaccine rollout once a candidate proves successful.

17. Pandemic Preparedness and Infrastructure

A key takeaway from the COVID-19 crisis is the necessity of strong surveillance networks and genomic sequencing platforms to identify and track viral mutations [32]. For NiV, leveraging next-generation sequencing can identify emergent variants or new spillover events in real time [33]. Pandemic preparedness frameworks encourage the stockpiling of vaccine doses and the creation of regional manufacturing hubs that can be rapidly activated [41]. Given that NiV outbreaks tend to be focal (e.g., localized in certain districts of Bangladesh or India), agile deployment of vaccine supplies—coupled with ring vaccination strategies—may effectively contain spread if combined with robust contact tracing [31].

18. Future Directions

18.1. Multivalent and Pan-Henipavirus Vaccines

There is growing interest in developing cross-protective vaccines that target shared epitopes between NiV and Hendra virus (HeV), collectively referred to as Henipaviruses [3,33,40]. The rationale is that HeV and NiV share critical glycoproteins (G and F) with overlapping epitopes; a single vaccine could theoretically protect against both pathogens, especially beneficial in regions with potential for either virus to emerge. Early studies on HeV-specific vaccines have indicated partial cross-neutralization against NiV, but broader coverage against multiple NiV strains (e.g., NiV-M and NiV-B) remains a challenge [40]. Building on these findings, advanced immunoinformatics methods could identify highly conserved domains of NiV-G that remain stable across variants and related henipaviruses, guiding rational vaccine design [36].

18.2. Advanced Adjuvants and Delivery Systems

Ongoing research into novel adjuvants—for instance, saponin-based systems or nanoparticle formulations that co-deliver immunostimulatory molecules—holds promise for enhancing NiV vaccine efficacy [33,43]. Such strategies can amplify local immune activation in draining lymph nodes and skew responses toward desired Th1 or Th2 phenotypes, depending on the nature of the antigen and disease [27,30]. Additionally, advanced delivery mechanisms, such as microneedle patches or self-amplifying mRNA vectors, could potentially simplify mass vaccination programs, particularly in remote or low-resource settings where conventional injection-based protocols can be logistically challenging [32].

18.3. Vaccine Hesitancy and Risk Communication

Historical lessons from Ebola and COVID-19 stress that efficacious vaccines are only part of the solution; acceptance within communities is equally pivotal [28,33]. In some endemic regions, cultural practices (such as the consumption of raw date palm sap) are deeply ingrained, making communication strategies that merely "warn people" insufficient. Effective risk communication demands culturally sensitive engagement with local communities, religious leaders, and healthcare workers. Transparent disclosure of vaccine trial data, side effects, and benefits is essential to foster trust [29,38]. Public outreach must also address the ethical dimensions of prioritizing certain high-risk groups—such as frontline healthcare workers or swine farmers—in the allocation of limited vaccine doses [31,33].

18.4. Long-Term Surveillance of Vaccine Recipients

Because NiV can cause lingering neurological sequelae, post-licensure surveillance of vaccine recipients should incorporate neurological assessments to confirm that the vaccine neither exacerbates nor induces neuroinflammatory conditions [30,35]. Such surveillance can be integrated into existing health information systems to track vaccine-related adverse events comprehensively. Mechanistic studies exploring the pathophysiology of NiV-induced encephalitis may also clarify if certain vaccine platforms offer additional neuroprotective benefits by curtailing viral spread to the central nervous system early in infection [36].

19. Clinical Translation and Policy Implications

As NiV vaccine candidates transition from preclinical proof-of-concept to human trials, partnerships between government agencies, academic laboratories, and pharmaceutical companies become indispensable [32,34]. The

complexities of NiV—ranging from its broad host range and variable incubation periods to the lack of large, continuous human outbreaks—imply that robust international coordination is needed for multi-site clinical evaluations. Funding mechanisms that prioritize neglected tropical diseases and emerging pathogens can facilitate these large-scale trials even in the absence of a worldwide NiV crisis [30].

A successful NiV vaccine would not only avert thousands of potential deaths but also safeguard agricultural sectors, particularly pig farming communities. Ensuring equitable distribution, especially in rural and lower-income regions most at risk of NiV outbreaks, represents a formidable challenge [33]. Policy frameworks akin to COVAX (the COVID-19 Vaccines Global Access facility) might serve as templates for pooling resources, accelerating manufacturing, and guaranteeing that vaccine doses reach resource-limited settings promptly [27,42].

Nipah virus stands as a formidable threat to global health, given its propensity for severe neurological and respiratory disease, high mortality, and documented person-to-person transmission. Amid these concerns, NiV-G has emerged as a critical focal point for vaccine design, given its indispensable role in viral attachment and entry. Leveraging cutting-edge structural biology, immunoinformatics, and innovative vaccine platforms—ranging from subunit formulations to nucleic acid approaches—researchers worldwide have made substantial strides in developing candidates that offer robust, cross-protective immunity.

Significant questions remain regarding the durability of immunity, the potential for immune escape via mutations in NiV-G, and the operational logistics of manufacturing and distributing NiV vaccines at scale. Moreover, the sporadic nature of NiV outbreaks complicates traditional efficacy trials, requiring the exploration of alternative regulatory pathways and adaptive trial designs. A truly comprehensive approach must also incorporate a "One Health" perspective, addressing bat reservoirs, intermediate hosts, and human behaviors that facilitate viral spillover.

Despite these obstacles, the progress achieved so far is notable. Lessons derived from other emerging pathogens, particularly the rapid vaccine development during the COVID-19 pandemic, demonstrate the feasibility of creating safe and effective vaccines under accelerated timelines when backed by global collaboration. Should current NiV vaccine prototypes prove successful in advanced clinical testing, they would represent a landmark achievement in pandemic preparedness—positioning humanity to mitigate or even prevent outbreaks of this lethal virus. These advances could, in turn, serve as a blueprint for tackling other high-consequence zoonotic threats, thereby reinforcing the foundational pillars of global health security.

Author Contributions

Conceptualization, M.M., I.G.Q., S.H.I., and N.A.; validation, S.H.I. and N.A.; formal analysis, M.M., I.G.Q., A.S., and H.H.N.; data curation, M.M., I.G.Q., A.S., and H.H.N.; writing—original draft preparation, M.M and I.G.Q.; writing—review and editing, S.H.I. and N.A. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declared no conflict of interest.

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