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Silent Threat of Nipah Virus (NIV) as a Re-Emerging zoonosis: Overview on Evolution and Impact, Pathogenesis, Transmission, and Molecular Mechanisms of NIV Entry and Replication

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Abstract

Nipah virus (NiV) is one of the emerging and deadly zoonotic virus threats to animal health, livestock production and ecological stability because of its complicated modes of transmission and serious disease consequences. Studies on animals have determined Pteropus bats to be natural reservoirs in which the virus is held in an asymptomatic manner allowing the virus to persist and be shed into the environment, and pigs which are critical amplifying hosts allowing the virus to be easily spread in densely populated livestock systems. Hamsters and ferrets have been useful experimental animal models that show the relationship to disease progression, such as intense respiratory disease, neurological dysfunction, and extensive vascular destruction that is indicative of systemic infection. NiV uses cellular entry via special host receptors ephrin-B2 ephrin-B3, which is mediated by concerted activity of viral glycoproteins, after which efficient replication and cell-to-cell transmission causes widespread tissue damage. Moreover, the virus demonstrates high immune evasion mechanisms and disrupts host interferon activation, the adaptive immune system, and increases its virulence. Nevertheless, the presence of interspecies variation, insufficient knowledge of immune tolerance in reservoir hosts, as well as restrictions related to recreating natural ecological conditions are still the challenges of importance. This review summarizes animal experimental data on the evolution, spread, pathogenesis, and molecular pathogenesis of NiV, its effects on animal systems, and the necessity to have better surveillance, advanced biosecurity frameworks, and develop effective vaccinations and therapeutic interventions.

Keywords: Nipah Virus, Zoonosis, Pteropus Bats, Animal Models, Pathogenesis, Viral Transmission, Ephrin Receptors, Immune Evasion.

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1. INTRODUCTION

Nipah virus (NiV), a member of the genus Henipavirus within the family Paramyxoviridae, has emerged as a significant re-emerging zoonotic pathogen with profound implications for animal health and ecological stability[1]. Primarily maintained in natural reservoirs such as fruit bats of the genus Pteropus, the virus persists asymptomatically in these hosts, enabling continuous circulation in nature. Environmental disturbances, including deforestation, urban expansion, and changes in agricultural practices, have intensified interactions between wildlife and domestic animals, thereby facilitating spillover events. In particular, pigs have been identified as key intermediate and amplifying hosts, where the virus can spread rapidly within dense populations, leading to severe outbreaks. Animal-based studies have demonstrated that NiV infection results in multi-organ involvement, including respiratory distress, neurological dysfunction, and vascular damage, highlighting its high pathogenic potential and complex disease profile[2].

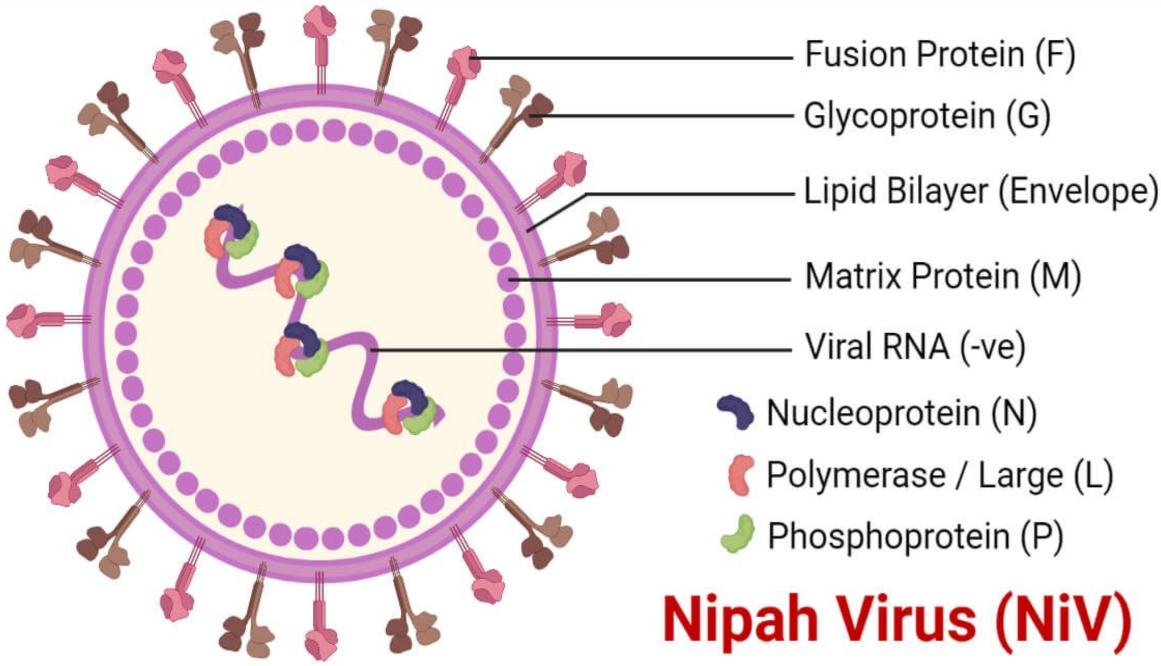

Figure 1: Nipah Virus (NIV)[3]

The aim of the review is to offer a clear insight into the little known but important threat that is Nipah virus, basing on the animal-related approach to the subject through evolutionary processes, transmission patterns, pathogenesis, and molecular processes of entry and replication of the virus[4]. The experimental models of bats, pigs, hamsters and ferrets have been used to provide insights that have been useful in understanding the host-virus interactions and disease progression. On the molecular level, NiV expresses certain host-specific receptors, including ephrin-B2 and ephrin-B3, to achieve cellular entry, and subsequently, active replication, which adds to extensive tissue damage. The knowledge of these mechanisms is important in the development of effective preventive and control measures. Since NiV is re-emerging and may have an effect on livestock systems and zoonotic transmission, animal model studies are necessary to enhance surveillance and biosecurity interventions, as well as inform future vaccine and therapeutic intervention developments[5].

1.1 Background and Context

NiV is a highly pathogenic and re-emerging zoonotic virus with a high potential threat to animal health and ecological stability and is a member of the genus Henipavirus of the family Paramyxoviridae[6]. It is mostly sustained in the natural reservoirs, including the fruit bats of the genus Pteropus that are infected by the virus without showing any symptoms and help to maintain the virus in nature. The cross-species transmission of the virus to domestic animals, especially pigs, identifies the presence of serious diseases with respiratory, neurological, and vascular problems. Habitat destruction, urbanization and more contact between wildlife and livestock are environmental changes which have greatly contributed to the occurrence and reoccurrence of NiV in animals[7].

1.2 Objectives of the Review

The main purpose of this review is:

- To examine the Pteropus bats as natural reservoirs and their role in the evolution and maintenance of the Nipah virus in the animal population.
- To analyze the routes of transmission of NiV in animals, direct contact, contaminated food, and animal-to-animal transmission, especially in pigs which act as amplifying hosts.
- To explore the pathogenesis of NiV in animal models by concentrating on respiratory, neurological and vascular manifestations.
- To identify the molecular processes of NiV entry and replication, the involvement of viral glycoproteins and host receptors (ephrin-B2 and ephrin-B3).
- To assess the response of the host immunity and viral immune evasion mechanisms in various animal models to aid in vaccine and therapeutic development.

1.3 Importance of the Topic

It is important to know Nipah virus in the view of animals because of the great influence it has on livestock health, agricultural systems and the occurrence of zoonotic diseases. The information gained through animal research will be critical in the development of efficient surveillance, enhance biosecurity and inform the design of vaccines and treatment interventions[8]. The issue of NiV as a re-emerging zoonosis is critical to reduce the future outbreaks and guarantee sustainable animal and population health management.

2. ANIMAL MODELS IN NIPAH VIRUS RESEARCH

Nipah virus (NiV) has been particularly investigated in animal models and animal-based research has been crucial in elucidating its transmission, pathogenesis, and host-disease interactions and as the natural reservoirs of the virus, Pteropus bats have been identified as an excellent animal model and pigs, hamsters, and ferrets have been the most useful animal models to study its pathogenesis, transmission, and host interactions and, with the support of in vivo studies, histopathology, molecular tests, and transmission studies, despite inherent limitations of interspecies differences[9].

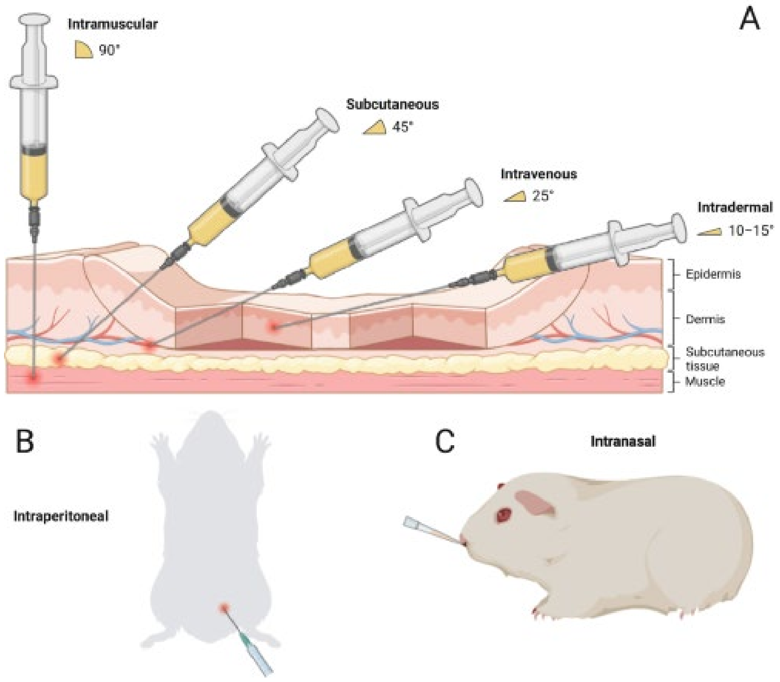

Figure 2: Animal Models in Nipah Virus[10]

2.1 Overview of Key Animal-Based Studies

A large number of studies conducted with the use of an animal model have offered important information about NiV biology, its modes of transmission, interaction with hosts and the course of the disease[11]. Research using Pteropus bats as the subjects of the study proves the idea of them being natural reservoirs because they carry the virus without any symptoms and shed the virus periodically through saliva, urine, and feces. These properties allow the virus to continue to persist in the population of the bats without any noticeable illness, which puts the idea of zoonotic spillover at risk. Pig experiments show that NiV causes notable respiratory disease, which increases the amplification of the virus and contributes to the effective spread in the context of high livestock densities, which makes pigs a significant intermediate host during epidemics[12].

NiV infection dynamics in small animal models like Syrian hamsters and ferrets have been extensively utilized as small animal models. The characteristics of these models are clinical such as respiratory distress, neurological dysfunction, and systemic vasculitis, which is highly comparable to the case of human infection[13]. Ferrets, especially, are deemed to be very acceptable as they can imitate the respiratory and neurological factors of the disease. Non-human primate models also confirm similar disease development and pathophysiology in humans though the review focuses on results in non-primate animal models because of their greater utility, cost-efficiency, and ethics[14].

2.2 Methodologies and Experimental Approaches

The NiV research on animals has various methodologies that are used to fully study the behavior of viruses, the host immune response and modes of transmission[15].

- **In vivo infection models:** The inoculation of bats, pigs, hamsters, and ferrets under controlled environments is done to study disease progression, viral replication, and clinical outcome under normal conditions. These models are useful in simulating natural infection pathways and give useful information about host-pathogen interactions.
- **Histopathological analysis:** Infection in tissues is characterized by endothelial injury, vasculitis, and specific lesions in different organs, especially lungs and central nervous system. These results are necessary in knowing the pathological basis of the NiV infection.
- **Molecular assays:** Detection of viral RNA and localization of the protein is performed with the help of RT-PCR and immunohistochemistry which allows specific identification of infected cells and quantifying the viral load in various tissues.
- **Transmission studies:** Cohousing experiments have shown horizontal spread between animals, and can be used to measure levels of viral shedding, levels of transmission efficiency and conditions that contribute to spread among populations.

These approaches in combination will enable a strong and complementary data on viral tropism, host immune response and efficiency of transmission, which will augment the overall knowledge in NiV pathogenesis[16].

2.3 Strengths and Limitations of Animal Studies

Strengths

The possibility of studying early stages of infection, viral replication and host immune responses, virtually impossible in humans, enables the animal models to conduct critical studies on how therapeutic treatments and prevention protocols are introduced and activated at the early stages of virus entry. Viruses that infect other cells and tissues Biology Animal models play a crucial role in preclinical testing of therapeutics and preventive interventions, as they can study the initiation of treatment and infection at the initial stages of virus entry[17].

Limitations

The fact that animal models might not accurately reflect the complexity of human disease may limit generalizability of study results to humans, since the environment and behavior cannot be easily recreated under laboratory conditions.Limiting scope and scalabilityBecause of ethical and logistical constraints in large animal studies, especially pigs and non-human primates, environmental and behavioral factors are not easily recreated[18].

3. EVOLUTION, TRANSMISSION, AND PATHOGENESIS OF NIPAH VIRUS IN ANIMAL SYSTEMS

The evolution of the Nipah virus (NiV) is tightly linked with the existence of pteropus bats as natural reservoirs, and the environmental stressors enhance the shedding of the virus and the further transmission in direct contact, contaminated feed, and animal-to-animal, especially in the case of pigs serving as amplifying hosts[19].

The efficiency of cellular penetration and viral replication in animal models results in extensive tissue damage and severe pathology caused by NiV, which has a severe respiratory, neurological, and vascular damage[20].

3.1 Evolution and Reservoir Dynamics

Pteropus bats are direct reservoir hosts of NiV and are important in keeping the virus in the natural environment[21]. According to genetic studies of the viral isolates that are found in bat populations, there is a high level of sequence conservation implying stable maintenance of the virus with occasional mutations that can affect host adaptability and virulence. Habitat loss, urbanization and food shortages are environmental stressors that have been observed to change the behavior and physiology of bats resulting in the increase of viral shedding. This increased shedding increases the probability of spillover to domestic animals and people thus contributes to the outbreak and re-occurrence of outbreaks[22].

Figure 3: Pteropus Bats[23]

3.2 Transmission Pathways in Animal Systems

NiV is transmitted in animal populations by a variety of interrelated mechanisms that enable within-species and between-species transmission to occur in a very short period:

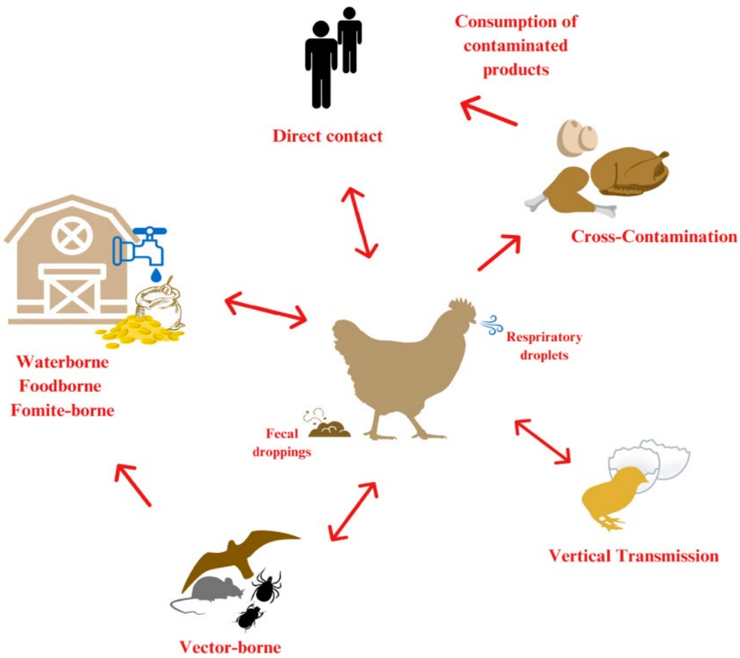

Figure 4: Transmission Pathways in Animal Systems[24]

- **Direct contact:** Contact with contaminated body fluids like saliva and urine between bats and livestock constitute one of the major modes of transmission particularly in places where livestock sharing of habitat occurs.
- **Contaminated feed:** Bats partially and contaminated fruits serve as a major source of infection to both pigs and other animals which place emphasis on the importance of environmental contamination.
- **Animal-to-animal spread:** The transmission is especially effective among pigs where respiratory secretions are the main mode of transmission which allows the virus to rapidly disseminate within highly crowded herds.

Practical studies also affirm that pigs are amplifying hosts and thus play a critical role in propagating the virus to human beings and other animals by considerably increasing viral load[25].

3.3 Pathogenesis in Animal Models

Infection of animals with NiV is associated with the involvement of multi-organs and a high severity of clinical symptoms similar to those of a human disease.

- **Respiratory involvement:** The infection usually causes intense inflammation of the lungs, edema and respiratory distress that are the key causes of morbidity.

- **Neurological manifestations:** The virus enters into the central nervous system causing encephalitis, neurological dysfunction and behavioral abnormalities.
- **Vascular damage:** Endothelial cell infection leads to extensive vasculitis, vascular permeability, and hemorrhage which add to the severity of the systemic disease.

Invariably, histopathology indicates the presence of the hallmark of paramyxoviruses infection, multinucleated syncytial cells, which transforms into the evidence of efficient cell-to-cell virus transmission and massive tissue destruction[26].

3.4 Molecular Mechanisms of NiV Entry

The two viral glycoproteins are essential in infection as they mediate NiV entry into the host cells:

- **Attachment glycoprotein (G):** The protein specifically binds to host cell receptors, ephrin-B2 and ephrin-B3 both of which are broadly distributed in endothelial and neuronal tissues.
- **Fusion protein (F):** After binding with the receptors, this protein facilitates fusion between the viral envelope and the host cell membrane which facilitates the entry of viral genetic material into the cell.

The presence of these molecular interactions allows NiV to infect a wide variety of host cells, especially those of the vascular and nervous systems, thus explaining its extensive tissue tropism and extreme pathogenicity in the body[27].

3.5 Viral Replication Mechanisms

After the virus enters the host cell, NiV follows a fast and successful step of replication that serves as an important contributor to the development of the disease. This occurs by the liberation of the viral RNA genome into cytoplasm where it act as a template to undergoes transcription and replication. The synthesis of viral proteins is an arrangement of the translational machinery of the host cell, and new viral particles are assembled. Such newly formed virions can then get discharged through the host cell membrane by means of budding and cause infection to neighboring cells.

It was proven in the animal studies that NiV replication is very effective and causes serious cytopathic effects, such as cell death and tissue injury, which influence the severity of infection and clinical outcome significantly.

4. HOST IMMUNE RESPONSE AND VIRAL IMMUNE EVASION IN ANIMAL MODELS

Differences in the susceptibility and severity of disease have been observed to be caused by animal-based studies, which found that there were specific patterns of host immune responses to Nipah virus (NiV) between different species. The NiV infection in natural reservoirs like Pteropus bats is usually asymptomatic, and this is ascribed to the controlled innate immune response. These bats are characterized by an equal balance in the production of interferons and antiviral proteins that are efficient in regulating the viral reproduction without causing excessive inflammatory reactions[28]. To the contrary, intermediate and experimental hosts (pigs, hamsters, ferrets) exhibit a more intensive and usually dysregulated immune response. The initial phases of infection in such animals are the engagement of innate immunity, namely, macrophages, dendritic cells, and the production of pro-inflammatory cytokines. Nevertheless, this reaction usually becomes an over-the-top inflammatory response, which leads to the destruction of tissues, especially those of the respiratory and nervous systems. Adaptive immune responses such as the generation of neutralizing antibodies and activation of T-cells have also been noted but in very cases, they are inadequate to stop systemic viral infection in the susceptible animal models.

Various strategies have been developed by NiV to avoid host immune defenses which have been best understood in animal models. Some of the proteins that are encoded by the virus include P, V, and W that disrupt the host interferon signaling pathways and suppress the antiviral response. These viral proteins prevent the production of various important signaling molecules that are important in the generation of interferon and activation of the immune response in infected animal models, which enables the virus to replicate successfully in the initial period of the infection. Also, NiV induces cell-to-cell fusion leading to the formation of multinucleated syncytia enhancing viral transmission at the lowest possible exposure to extracellular immune factors including neutralizing antibodies[29]. Experiments in hamsters and ferrets have also revealed that NiV can postpone the development of adaptive immunity, and this gives a serious time to viral spreading. The difference in host specific immune regulation lies in the fact that immune tolerance in bats and immune-mediated pathology in other animals is markedly different. These mechanisms learnt in animal models would be important in the development of specific immunotherapeutic and vaccines to control the NiV infection.

Table 1: Literature Review on Zoonotic Viral Diseases and Nipah Virus Research[30]

Author(s) & Year	Study Title	Focus Area	Methodology	Key Findings
Samad (2025)[31]	Emerging and Re-emerging Zoonotic Viral Diseases with a One Health Perspective in Bangladesh	Zoonotic diseases and One Health framework	Long-term review (58 years) of zoonotic disease patterns	Highlighted interconnected human-animal-environment health; identified ecological disruption, climate change, and human-animal interaction as

				key drivers; emphasized integrated surveillance and multidisciplinary approaches.
Sannathimmappa, Nambiar & Patil (2021)[32]	Emerging and Re-emerging Viral Infections in the 21st Century: Microbiological and Public Health Perspectives	Viral infections and public health	Review-based study	Identified globalization, urbanization, and environmental changes as major drivers; stressed importance of early detection, advanced diagnostics, and strong healthcare systems.
Satapathy et al. (2025)[33]	Nipah Virus at the Human-Animal-Environment Interface	NiV transmission, neurotropism, and pandemic risk	Analytical review of ecological and biological data	Emphasized role of bat reservoirs and intermediate hosts; highlighted neurotropism and severe encephalitis; stressed importance of understanding spillover dynamics for outbreak prediction.
Sheikh & Raza (2021)[34]	Viroinformatics and Viral Diseases: Translational Bioinformatics	Computational virology and bioinformatics	Conceptual and analytical review	Demonstrated use of computational tools in studying viral genomes

	Applications in Healthcare			and host interactions; improved surveillance, vaccine design, and therapeutic development.
Sheikh & Raza (2021)[35]	Viroinformatics and Viral Diseases: An Interdisciplinary Approach	Interdisciplinary viroinformatics	Conceptual review	Highlighted integration of virology, computational biology, and data science; emphasized understanding of viral mechanisms, mutations, and epidemiological trends; supported evidence-based public health decisions.

5. DISCUSSION

In animal studies, it is shown that Nipah virus is a highly adaptive Zoonotic pathogen that has been sustained in Pteropus bats and amplified in pigs with experimental models showing that Nipah virus is a severe multi organ pathogen with efficient mechanisms of infection and immune tolerance identification; gaps in knowledge about Nipah virus include the dynamics of animal transmission, and limitations to animal models, which suggest that advanced research is necessary to enhance surveillance, vaccine development, and effective control methods[36].

5.1 Interpretation and Analysis of Findings

All the animal-derived results indicate that Nipah virus (NiV) has a very flexible and multi-host transmission system[37]. Peteropus bats play a role as efficient natural reservoirs where the virus has no or minimal pathological effect because of the balancing effect of immunity, whereas pigs are a key amplifying host that increases the viral transmissions in the populations of animals. Hamsters and ferrets are experimental models that can be used to replicate the main symptoms of the disease, including respiratory, neurological, and vascular, proving the systemic character of NiV infection. Additional molecular data also emphasizes the fact that the virus has large tissue tropism due to its binding of ephrin-B2 and ephrin-B3 receptors, along with a fast multiplication and efficient cell-to-cell infection. These combined results highlight the close connection between viral molecular events and host-specific reactions in the course of defining the severity of the disease and transmission profiles.

5.2 Implications and Significance

The lessons learned in animal research are important in the control and prevention of diseases. The discovery of bats as reservoirs and pigs as amplifying hosts demonstrates the significance of observing the wildlife-livestock interface to avoid the outbreak occurrence[38]. The knowledge of transmission routes e.g., contaminated feed, and direct contact can give a scientific level of understanding in the implementation of better hygiene measures and biosecurity in the farms as well as management of livestock. Also, the comprehensive knowledge of the pathogenesis and immune evasion processes can be used to create specific vaccines and antiviral treatments. Practically, animal models will continue being an irreplaceable aspect of preclinical testing, which would lead to safer and more efficient intervention measures in NiV outbreak management.

5.3 Research Gaps

Nevertheless, there are a number of significant gaps in the current animal-based research despite major development. It is not well understood how the mechanisms of Pteropus bat tolerance to NiV infection without devastating disease are maintained, especially the long time viral maintenance and immune regulation[39]. Existing animal models though informative are not complete to replicate natural ecological situations and the complexity of transmission processes in the real world situations. Moreover, the differences in interspecies immune responses create a problem of extrapolation of results to other hosts. The nature of chronic infections stages and subclinical transmission of the virus in animal population remains limited also which limits a complete realization of the viral maintenance and its transmission.

5.4 Future Research Directions

Future studies ought to focus on longitudinal ecological research on bat populations to understand better viral maintenance, shedding and environmental triggers. There is a necessity to create more sophisticated and representative animal models, which replicate the natural course of infection and conditions of transmission quite closely[40]. Research on the role of host immune responses especially immune tolerance in reservoir hosts and immune deregulation in susceptible animals will be critical in identifying new therapeutic targets. Also, a combination of molecular, ecological, and experimental methods can be applied to make the predictive modeling and early-detection models more robust, and, eventually, more effective in managing and preventing NiV outbreaks in animals.

6. CONCLUSION

To summarize, Nipah virus (NiV) remains a severe and dynamic zoonotic threat impacting animal systems due to its capacity to remain asymptomatic in Pteropus bats and multiply effectively in intermediate hosts like pigs, therefore, facilitating speedy interspecies transmission. The use of animals in the research has been invaluable in understanding the evolutionary stability of the virus, the route of the virus and also in pathogenesis, which is complex and critical as evidenced by its ability to cause severe respiratory, neurological, and vascular damage due to its ability to enter host cells effectively, multiply within them, and evade the immune system highly. The results highlight the significance of molecular interactions, ephrin receptors and viral glycoproteins, in the process of setting the severity of the disease and the vulnerability of the host. Nonetheless, some major gaps still exist, such as the lack of knowledge of immune tolerance in reservoir hosts, the inability to recreate natural ecological conditions, and the interchangeability of responses in various animal models. The mitigation of these constraints by consideration of cutting-edge experimentation methods, prolonged ecological investigations, and combined molecular examination is needed to enhance the process of disease monitoring, enhance livestock system biosecurity, and enable the creation of efficient vaccines and therapeutic measures to restrain and forestall eventual NiV outbreaks.

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