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The Current Pathogenicity and Potential Risk Assessment of Nipah Virus as Potential Cause of "Disease X": A Narrative Review

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ABSTRACT

Background and Aims: The World Health Organization (WHO) recognized the potential for a severe international epidemic and introduced the term "Disease X" to classify pathogens that not yet identified. The Nipah virus (NiV) is highly dangerous due to its zoonotic nature, high mortality rate, and ability to cause severe clinical symptoms in humans. In this review, we gather the latest information on the NiV and its potential to become a significant candidate for Disease X.

Methods: We performed a thorough review of articles published in PubMed, Scopus, and Google Scholar using appropriate MeSH terms and keywords. Studies reported NiV infection were considered for this review.

Results: The NiV exhibits different epidemiological patterns in different countries that calls for customized prevention and control strategies. Genetic analysis highlights NiV's ability to mutate that alters possible treatment options. Transmission typically involves bats as the primary reservoir, with humans becoming infected either through intermediate hosts or food. This shows NiV's complex nature, including its ability to reach the central nervous system through the olfactory nerve. Promising treatment options, such as monoclonal antibodies, antivirals, and ongoing vaccine research, provide hope. However, the virus's adaptability, human-to-human transmission, and the lack of specific antiviral therapy raise concerns about its potential to cause a global pandemic. The interconnection between animals, humans, and the environment stresses the need for a One Health approach to tackle emerging infectious disease by NiV.

Conclusion: Global collaboration, surveillance, and research investments are imperative for the preparation of future pandemics. The ongoing COVID-19 challenges underscoring the critical need for sustained scientific endeavors, global leadership, and recognition of the prominence of NiV as a candidate for the potential Disease X.

1 | Introduction

In 2018, the World Health Organization (WHO) acknowledged the probability of a "serious international epidemic caused by a pathogen not presently identified as a human disease agent." To address this potential threat, a new classification was introduced to the emergency priority list known as Disease X [1]. Several experts suggest that COVID-19, caused by the SARS-CoV-2 virus, meets the criteria to be considered the first "Disease X." Meanwhile, other authors have also identified Zika as another potential candidate for this classification [2, 3]. The objective is to comprehend and identify potential pathogens in advance, facilitating the development of strategies, vaccines, and treatments to effectively manage and mitigate the impact of future

outbreaks. Pathogen X has a broad spectrum, encompassing various pathogens which includes parasites, bacteria, fungi, viruses, prions or parasites [4]. Among the 400 recognized emerging infectious disease events since 1940, the bacterial infection account for 54%, while the viral or prion pathogens make up 25%, protozoal infection 11%, fungal infection 6%, and helminths 3% [5]. While viral pathogens constitute a smaller proportion among infectious diseases, some of the most distressing recent events, including HIV, influenza H5N1 and H1N1, COVID-19, Ebola virus, Lassa virus, and Middle East respiratory syndrome coronavirus, have found to be associated with RNA viruses [6].

The Nipah virus (NiV) is a paramyxovirus that causes a zoonotic disease with a high mortality rate. Consequently, it has been designated as a Blueprint priority pathogen. Bats serve as the primary reservoirs for this virus, and various clinical manifestations have been reported in humans [7]. The NiV infection is a viral disease that has appeared in Southeast Asia. It is caused by a single-stranded RNA virus with 18,000 nucleotides long and belongs to the Henipavirus family. This family also includes other viruses that can infect people, such as the Ghanaian bat virus, Mojiang virus, and Hendra virus (HeV) [8]. The high death rates in humans linked to NiV, which can be as high as 70% case fatality rate, have resulted in these viruses being labeled as risk-group 4 pathogens. This means that research on them can only be done in Biosafety Level 4 (BSL-4) labs. The BSL levels consider how deadly the disease is and whether there are any preventive or treatment options available. Currently, there are no treatments for NiV or HeV, even though their genomes are about 80% alike. This striking similarity emphasizes the urgent need for global surveillance, research, and collaboration to stay ahead of emerging infectious threats. Adding to the concern, scientists predict that Pathogen X could pose a serious danger due to its ability to replicate across multiple host species. Its highly error-prone reverse transcriptase drives rapid mutations, allowing it to escape body's defenses. To make matters worse, a staggering 94% of zoonotic viruses affecting humans are RNA-based, further underlining the threat [5, 9–11]. Therefore, here we aimed to assess the pathogenicity and potential risks of NiV to cause public health emergency of international concern.

2 | Method

We performed a comprehensive literature search in the PubMed database according to the following search terms: (“Nipah virus infection” or “Henipavirus Infections”) and (incidence or deaths or mortality or case-fatality) and (infectious disease outbreak or viral infection). Based on the available published articles, we evaluated the high-quality evidence for this review.

3 | Disease Epidemiology

The NiV has manifested differently in various countries, with distinct epidemiological patterns. In Malaysia, the virus was isolated from the cerebrospinal fluid sample of NiV affected patient in Sungai Nipah village (Malaysia). Serological studies have shown that animals (e.g., cows, horses, dogs, cats, goats, etc.) can be exposed to NiV and can produce specific antibodies against it. However, there have been no reports of these animals transmitting the virus to humans [12–14]. Control measures, including culling over a million pigs, were implemented successfully. Dogs were also found infected, but no human-to-human transmission occurred. Eventually, *Pteropus* bats were identified as the reservoir in Malaysia [15]. In Bangladesh, seasonal NiV outbreaks have occurred since 2001 during the winter season near central and northwestern parts of Bangladesh, primarily in the ‘Nipah belt.’ *Pteropus* bats act as the reservoir, with transmission often linked to drinking raw date palm sap during sap harvesting season. Bats contaminate sap with urine or feces, and other domestic animals may contribute to transmission. Person-to-person spread is noteworthy, with the virus spread via droplet infection. The 2004 Faridpur outbreak of Bangladesh highlighted the largest person-to-person transmission event. The primary mode of transmission is considered the date palm sap consumption and person-to-person contact. Considering the timeframe between 2001 and 2016, the number of reported cases was found 67, and also noticed a declined number of affected people due to a mass awareness campaign after 2016 [16]. India experienced NiV outbreaks in 2001 (West Bengal and Siliguri), 2007 (Nadia district, West Bengal), and 2018 (Kerala) leading to the 45 deaths and 66 people being affected. Person-to-person transmission occurred in every Indian outbreak. The 2018 outbreak in Kerala, geographically distant from previous cases, had no common date palm sap consumption. The virus spread in healthcare settings, emphasizing the potential for nosocomial transmission. The 2001 Siliguri outbreak originated in a district hospital, affecting staff and visitors. Limited reported outbreaks in India hinder definitive epidemiological conclusions [7]. In the Philippines in 2014, a NiV outbreak resulted in 17 confirmed cases with a high rate of fatality rate (82% cases). Ten patients had reported contact with horses or consumed horse meat, suggesting a link to the virus. Person-to-person transmission occurred, a rarity in strains related to the Malaysian variant. This indicated the possibility of strain coevolution or mutation, emphasizing the dynamic nature of the virus [15].

4 | Genetic Mutations of Virus

NiV is an evolving *Paramyxovirus* known for causing severe respiratory illness and fatal encephalitis in infected patient. Classified in the *Henipavirus* genus, NiV has a negative-sense, single-stranded RNA genome with helical symmetry. The genome comprises six genes: phosphoprotein (P), nucleocapsid (N), matrix (M), attachment glycoprotein (G), fusion glycoprotein (F), and long polymerase (L), forming the virus ribonucleoprotein. The fusion and glycoproteins play essential roles in cellular attachment and host cell entry, with the precursor fusion protein (F0) undergoing cleavage to initiate viral membrane fusion (F1 and F2). The M protein is crucial for morphogenesis and budding. Neutralizing NiV infectivity requires antibodies to the G protein. Coordinated action between F and G glycoproteins facilitates viral entry into host cells. Interactions between host cell B2/3 ephrin and NiV glycoprotein trigger conformational changes, activating F glycoprotein and initiating membrane fusion. NiV's intensified pathogenicity is

linked to its replication and fusion strategies involving ephrin receptors. *Henipaviruses* also encode multiple accessory proteins aiding in evading host immune responses [17, 18].

The Indian NiV isolate exhibited nucleotide and amino acid identities of approximately 97% and 95% with NiV-B (Bangladesh variant) sequences, and 91% and 83% with NiV-M (Malaysian variant) sequences, respectively. Amino acid substitutions in structural and nonstructural proteins, showed variations, particularly in the N, P/V/W, C, and L proteins. Notably, conserved regions important for capsid assembly and binding to STAT proteins demonstrated variations in NiV-B, while the Indian isolate maintained conservation in essential regions. No mutations were found in crucial regions of G and F proteins, indicating stable fusion and protein trafficking. The glycoprotein mutations affecting m102.4 monoclonal antibody binding were absent in Indian isolate, aligning with NiV-B sequences in the L protein [19–21]. Understanding these varied patterns is crucial for effective prevention and control strategies [15].

5 | Transmission and Spread

Comprehending the hosts and pathways through which viral diseases spread is crucial for managing epidemics. Bats, the second-largest mammal order, harbor over 200 viruses, some of which pose a significant threat to humans, such as rabies, Ebola, SARS, NiV, and HeV. NiV is transmitted among bat populations through close contact, and its transmission to humans typically involves intermediate hosts (pigs and horses) or the consumption of date palm sap contaminated by bat saliva or urine as shown in Figure 1. Incidents of NiV transmission from bats to humans have been documented in various locations. In Malaysia, individuals exhibited severe influenza-like symptoms after handling NiV-infected swine, while in the Philippines, people were infected through activities like horse butchering or consuming horsemeat. Human-to-human transmission of NiV was identified in India in 2001, and in Bangladesh, where palm sap is consumed, frequent NiV infections and person-to-person transmission have occurred. Despite preventive measures such as "bamboo skirts or lime on date palm trees" to limit bat access to sap, ongoing efforts are necessary to prevent NiV transmission and address potential risks associated with bat-to-human transmission through date palm sap [17].

Recent studies using aerosolized NiV in Syrian hamsters suggest potential transmission via NiV droplets during close contact. In Bangladesh, three NiV transmission pathways were identified: intake of fresh date palm sap or the fermented date palm juice known as tari, and preventing bat access to sap is crucial for averting NiV infections. Infrared camera studies showed bats, especially *Pteropus giganteus*, frequently visiting and licking date palm trees during sap collection. The virus can persist for days in sugar-rich solutions. An outbreak in Tangail district, Bangladesh, linked to raw date palm sap consumption, indicated symptoms during the sap collection season from December to March. High anti-Nipah viral antibody seroprevalence in *Pteropus spp*. suggests adaptation for transmission among bats. Interviews in Bangladesh from May to December 2004 revealed NiV transmission from bats to humans and between humans. Some communities attributed NiV infections to supernatural causes, emphasizing the need for spiritual strategies alongside medical interventions. Secondary human-to-human transmission occurred during outbreaks, with NiV shedding from bats initiating epidemics through person-to-person transmission. Patient handling and contact with infected secretions are identified as risk factors [17].

6 | Disease Pathogenesis

In NiV infection, the initial stage, the detection occurs in bronchioles, and viral antigens are found in the lungs, triggering

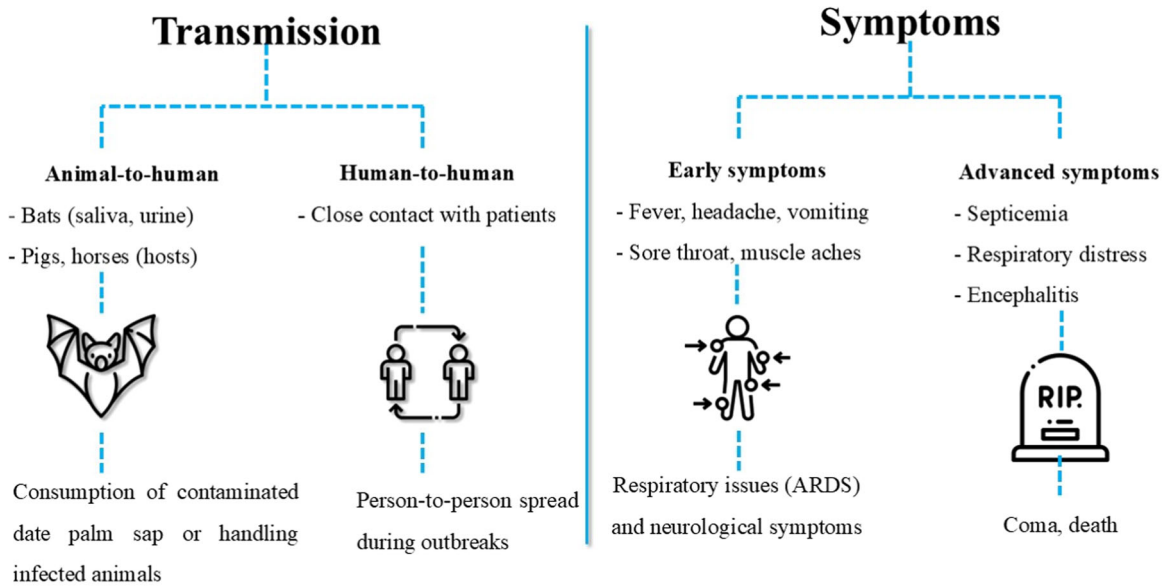

FIGURE 1 | Overview of transmission routes and symptoms. This figure illustrates the modes of transmission for the virus, distinguishing between animal-to-human and human-to-human pathways. It also categorizes symptoms into early and advanced stages, highlighting critical health concerns associated with the infection, including potential outcomes such as septicemia and death. Early symptoms may lead to respiratory issues (acute respiratory distress syndrome—ARDS) and neurological symptoms.

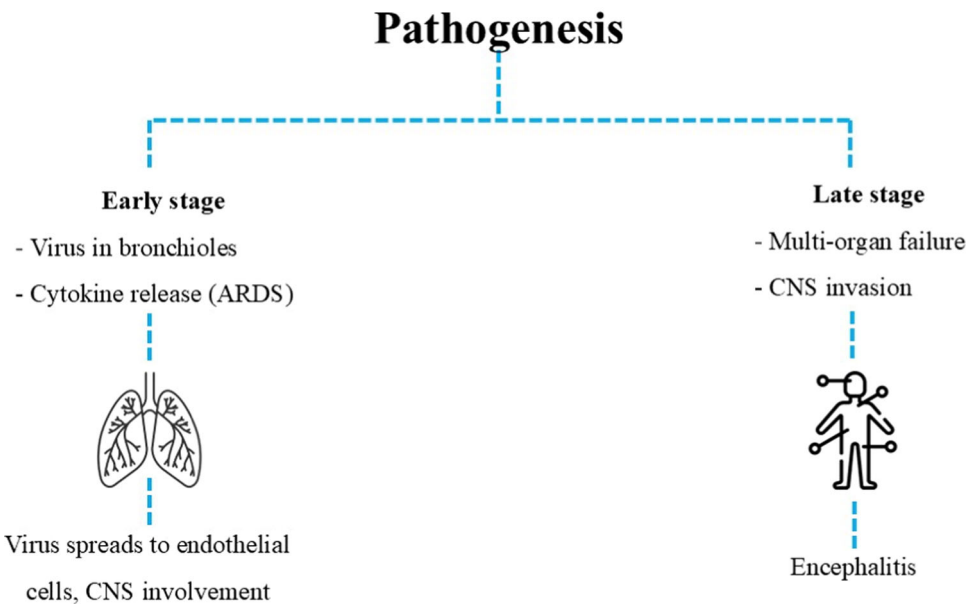

FIGURE 2 | Pathogenesis of the virus. This figure outlines the stages of pathogenesis, detailing the early and late stages of infection. In the early stage, the virus infects bronchioles, leading to cytokine release and acute respiratory distress syndrome (ARDS). As the disease progresses to the late stage, it can result in multiorgan failure and CNS invasion, potentially causing encephalitis.

cytokine release and leading to an ARDS-like disorder as shown in Figure 2. In later stages, inflammatory mediators are released, and the virus spreads to endothelial cells, causing multiorgan failure. NiV enhances the inflammatory process, leading to severe complications or death, primarily through a multiorgan vasculitis, which involves the infection of endothelial cells. This inflammation is most severe in the central nervous system (CNS), where vasculitis causes damage to the endothelial cells, mural necrosis, and infiltration of immune cells like polymorphonuclear leukocytes and mononuclear cells. These processes can result in severe encephalitis, respiratory distress, and neurological damage. The infection spreads to other organs, including the lungs, heart, spleen, and kidneys, leading to widespread inflammation and organ dysfunction, which contributes to the high mortality rates observed in outbreaks, especially where supportive care is limited [22–24]. In hamster models, NiV infects leukocytes, and it enters the CNS, disrupting the blood-brain barrier (BBB). Recent studies propose immediate virus entry into the CNS through the olfactory nerve, highlighting the multifaceted nature of NiV infection [25].

In the early stages, individuals may exhibit initial symptoms such as fever, headache, vomiting, sore throat, cough, and muscle aches. The condition may progress to septicemia, characterized by renal impairment and gastrointestinal bleeding. Some individuals may experience respiratory difficulties, ranging from unusual pneumonia to acute respiratory distress. As the illness advances, more severe symptoms like disorientation, drowsiness, mental confusion, seizures, and neurological signs indicative of encephalitis (brain swelling) may become apparent. The disease can rapidly escalate, resulting in coma and death within a matter of days. Statistical data indicates a mortality rate of approximately 40%–75% for this viral ailment. Survivors of the NiV may grapple with persistent side effects such as convulsions, changes in personality, and other enduring neurological disorders [17].

Since 2001, NiV outbreaks in Bangladesh have occurred seasonally from December to May, correlating with DPS harvesting (November to March). Reported cases ranged from 0 to 67 until 2016, decreasing due to an awareness campaign against raw DPS consumption. However, from January 2013 to February 2023, 11 cases (10 confirmed, one probable) and eight deaths were reported, the highest since 2015. Dhaka reported six cases, and Rajshahi reported five, with a concerning 73% case fatality rate. Of the 11 cases (four females, seven males, median age 16), 10 had a raw DPS drinking history. The median incubation period was 14 days, and all cases were hospitalized post-symptoms [16].

7 | Therapeutic and Preventive Measures

The monoclonal antibody m102.4, which demonstrates cross-reactivity in humans, emerges as a promising therapeutic option for NiV infection, showing effectiveness against both NiV and HeV. In ferret and nonhuman primate models, a single intravenous infusion of m102.4 offers complete protection, even when administered after exposure, underscoring its considerable potential. The compassionate use of m102.4 in high-risk situations involving *Henipaviruses*, with no reported adverse effects, justifies its advancement to a phase I clinical trial. The trial affirms the safety, tolerability, and sustained virus-neutralizing activity of m102.4, establishing it as a valuable therapeutic option for individuals exposed to *Henipaviruses* [26].

The experimental antibody therapy, h5B3.1, is a humanized monoclonal antibody designed to target the fusion protein F of both NiV and HeV. Demonstrating protective efficacy in ferrets, h5B3.1 is proposed as a potential therapeutic. Researchers recommend a combination approach by integrating h5B3.1 with m102.4 to target multiple viral surface glycoproteins and minimize the risk of escape mutants. However, due to limited

in vivo characterization, further studies are necessary before contemplating its introduction in human patients, either as a standalone treatment or in conjunction with m102.4 [27].

A broad-spectrum nucleoside analog, Ribavirin, stands out as the only clinically utilized therapeutic in NiV patients, showing a 36% reduction in mortality during the 1998/1999 outbreak in Malaysia. However, its efficacy during the 2018 Kerala outbreak remains inconclusive, with a 20% reduction in mortality. Other antivirals like remdesivir, favipiravir, and griffithsin show promise in small animal models, while various derivatives and fusion inhibitors exhibit varying degrees of efficacy in vitro. Defective interfering particles (DIPs) emerge as a potential strategy for inhibiting NiV replication in vitro, requiring further animal studies [27].

Suggesting a potentially effective treatment for NiV, the proposal involves combining monoclonal antibodies with small molecule antivirals. Four vaccine candidates show promise, with a HeV glycoprotein subunit vaccine currently in phase I clinical trials and three recombinant viral vector vaccines in preclinical development. Funding for these candidates has been provided by the "Coalition of Epidemic Preparedness Innovation (CEPI)." The emergence of mRNA vaccine technology is viewed optimistically, supported by the success of a nucleoside-modified mRNA vaccine that protected 70% of Syrian hamsters from a lethal NiV challenge [20]. Despite uncertainties about NiV transmission, guidelines for protecting healthcare workers emphasize standard infection control measures, isolation, and precautions. Hospitals in at-risk areas should be prepared for NiV cases, implementing screening, triage, and visitor management. Hygiene maintenance of hand and proper use of personal protective equipment (PPE) are crucial, and drug trials, especially for ribavirin, await clarification. The ultimate goal is humanity's triumph over the virus [28].

8 | Past Prevention Strategies and Lessons Learned So Far

According to the WHO, the One Health concept is a way to balance and improve the health of people, animals, and the environment. It brings together different sectors and communities to prevent, predict, detect, and respond to global health threats like pandemics. This approach combines public health, veterinary health, and environmental science, making it useful for better monitoring of NiV and reducing the risk of large outbreaks [29]. NiV outbreaks happen regularly in India and Southeast Asia. To prepare for potential pandemics, it's important to monitor NiV in these areas using tailored diagnostic tests and a One Health approach [7, 29]. NiV poses a significant threat to both animal and human health for several reasons: its main reservoir, Pteropodidae bats, are widely found in densely populated areas of Southeast Asia; the virus can be transmitted directly to humans from bats or domestic animals; human-to-human transmission is possible; outbreaks often occur in crowded areas; the mortality rate is hi h; and there is no effective vaccine or treatment. These factors make NiV a top priority pathogen for the WHO, highlighting the importance of the One Health approach for preparedness. Since the SARS-CoV-2 pandemic, this method has become increasingly important for managing infectious diseases, as prevention and preparedness help us understand and limit pandemic risks.

The close relationship between humans and animals means that activities like wildlife trade, hunting, deforestation, climate change, intensive agriculture, and urbanization increase contact between the two and raise the risk of viral outbreaks. For instance, recent reports from Vietnam indicate a potential emergence of new zoonotic viruses in bats due to close human–animal interactions. Effective spillover surveillance is key to preparing for new viruses. This involves assessing risks, monitoring wildlife and farms (such as pigs and poultry), and connecting this data to human health information. Such an approach can help implement containment measures quickly [7, 14, 25, 29].

Animal markets in Asia are well-known hotspots for viral outbreaks, especially since bats, which carry NiV, are often sold in street markets. Studying the NiV genome in bats through PCR testing and seroprevalence studies can help track how the virus spreads and how human outbreaks start. Four factors must be present to trigger an epidemic: the intensity of transmission in bats, the dynamics of that transmission, the shedding of the virus, and human contact with bats, often through food consumption [30, 31]. All activities that bring animals and humans together should be monitored in countries at risk for NiV, but various challenges exist, including organizational, financial, logistical, and technical issues. A successful strategy used in Vietnam focused on preparing for health surveillance in wildlife, domestic animals, and humans. This can help identify areas with the highest emergence risk [100]. In Kerala, India, a team of public health experts, microbiologists, and infectious disease specialists works together to verify diagnoses, control outbreaks, and identify sources of infection. They collect and identify bats, ensure quick access to PPE, and implement logistics to rapidly limit person-to-person transmission during spillover events [32]. For a successful strategy, as seen in India, preparation must take place before a NiV emergency occurs. This involves building solid collaborations between human and animal health institutions to detect early warning signs and develop faster public health responses when an emergency arises [29, 32]. Therefore, applying the One Health approach to NiV is particularly important for preventing outbreaks and reducing their impact.

9 | Prediction to Cause Global Pandemics

Belonging to the Henipavirus genus, the NiV has been linked to severe respiratory illness and encephalitis in various species, including humans. The fruit bats of the *Pteropus* genus, known as flying foxes, are recognized as the primary natural reservoirs of NiV. The virus has been found in bat urine and partially consumed fruit, indicating a potential route of direct transmission from flying bats to humans through contaminated food sources [17].

The virus has shown the ability for human-to-human transmission, particularly within healthcare settings, raising concerns about sustained transmission in densely populated areas, associated with a high fatality rate, ranging from 40% to 75%, and there is a lack of specific antiviral treatments, amplifying

the potential health impact during outbreaks. The virus has been identified in several countries in Southeast Asia, and its zoonotic nature, combined with global connectivity through increased travel, enhances the risk of a pandemic. The virus's adaptability and potential for evolution further contribute to the unpredictable nature of NiV outbreaks [9, 29, 32, 33].

The potential threat of the *Henipavirus* strain NiV, which has caused multiple outbreaks over 22 years. There is speculation that NiV could be the next pandemic after COVID-19. The author stresses the importance of a One Health approach, focusing on the interconnectedness of animal, human, and environmental factors. Strategies proposed include surveillance of animal health, monitoring human and environmental health, ensuring food safety, addressing environmental issues, and promoting global collaboration. The absence of specific antiviral drugs and vaccines, along with the need for continued research in various areas, emphasizes the importance of being prepared and vigilant. To predict and reduce the risk of a pandemic caused by NiV outbreaks, it is essential to track their genetic changes, understand how they spread, and develop treatment and prevention strategies [34]. Achieving these goals will require global teamwork and ongoing research efforts. The text also underscores the need for continued scientific efforts, investment in virus and vaccine research, and global leadership to prepare for future pandemics. The ongoing challenges of the COVID-19 pandemic highlight the limitations of healthcare systems worldwide [35].

10 | Conclusion

The emergence of Disease X highlighted by the WHO shows a possible global health crisis caused by unknown pathogens. The COVID-19 pandemic reminded us how urgent it is to watch for new health threats and work together to fight them. Pathogen X could include viruses, bacteria, fungi, parasites, or prions, which means we need broad and careful strategies. NiV, with its different patterns in various regions, requires prevention and control measures that are suited to each location. Therefore, applying the One Health approach to NiV is especially important for stopping outbreaks and reducing their effects. Early detection, stronger healthcare systems, and multiple strategies are essential to contain outbreaks and reduce their global impact.

Author Contributions

Samiha Mehnaz: conceptualization, methodology, data curation, writing–original draft. **Ramisa Anjum:** conceptualization, methodology, data curation, writing–original draft. **Fatema Rahman Mithila:** conceptualization, methodology, data curation, writing–original draft. **Syed Masudur Rahman Dewan:** conceptualization, methodology, supervision, validation, writing–review and editing. **Md. Rabiul Islam:** methodology, conceptualization, writing–review and editing, supervision, validation.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics Statement

It was an analysis of online available aggregate data. No Ethical approval was needed.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Transparency Statement

The lead author Samiha Mehnaz affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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