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MINI-REVIEW

Nipah virus: pathogenesis, genome, diagnosis, and treatment

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Abstract

The highly infectious Nipah virus (NiV) is classified under the Paramyxoviridae family and is categorized under the genus Henipavirus. NiV spreads to humans through zoonotic transmission from reservoir host bats and other intermediate hosts. It is highly contagious and has a high case fatality rate (CFR) of ~40–80%. Only sporadic outbreaks have been reported so far, but like SARS-CoV2, NiV has a high pandemic potential and has been put on the World Health Organization (WHO) priority pathogen list. Currently, no clinically approved antivirals, immunotherapy, or vaccines are available to tackle NiV infection, thereby necessitating further research into its life cycle, transmission, and pathogenesis. This detailed review outlines the origin and spread of the Nipah virus, its modes of transmission, risk factors, its genome, key proteins, pathogenesis, and clinical features. We also discuss different diagnostic approaches and ongoing research to develop therapies ranging from antibodies to vaccines.

Key points

- *Pandemic preparedness for emerging and re-emerging viruses.*
- *Novel approaches for diagnostics and therapeutics for Nipah viruse.*
- *Global threat from biosafety level 4 pathogens.*
- *Animal models for Nipah virus research.*

Keywords Nipah virus · Henipavirus · Viral outbreaks · Viral encephalitis · Anti-viral drugs · Clinical trials · Vaccines · WHO

Introduction

The emergence of novel pathogenic viral strains and their outbreaks has been reported more frequently in the last few decades, possibly due to rapid urbanization and changing climatic conditions. Newly emerging viruses such as Ebola virus, Crimean Congo hemorrhagic fever (CCHF) virus, Zika virus, swine flu virus, Lassa fever virus, Marburg virus, coronaviruses, Nipah virus (NiV), and Rift Valley fever (RVF) virus, are serious threats to human health and have been classified as pathogens of global concern (Rizzardini et al. 2018). Their ability to spread quickly may lead to an international public health crisis similar to COVID- 19 (Sweileh 2017). These viral outbreaks are responsible for high mortality, morbidity, and economic burden worldwide. Old viruses such as influenza have the potential to resurface and pose new epidemic and pandemic threats (Taubenberger and Morens 2010). Viruses employ various strategies to infect humans, either by direct or by indirect means or through different reservoir host animals. Despite implementing stringent precautionary measures, the COVID- 19 pandemic appeared to be virtually unstoppable, leading to its spread throughout the globe. Similar to SARS-CoV- 2, many viral pathogens with increased propensity for causing an epidemic, such as NiV, Ebola, and Middle East respiratory

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coronavirus (MERS-CoV), originated from bats, and later spread by cross-species transmission through intermediate hosts (Mohd et al. 2016; Zhou et al. 2020; Letko et al. 2020).

NiV is a zoonotic single-stranded RNA-genome containing bat-borne pathogen of the family Paramyxoviridae. The other human pathogenic viruses of this family are Hendra virus (HeV), measles virus, human parainfluenza virus, and mumps virus (Ksiazek et al. 2011). It has the potential to trigger severe acute respiratory infection as well as encephalitis (Bellini et al. 2005). NiV is listed as a class C pathogen in the classification of pathogens. According to the Centers for Disease Control and Prevention (CDC) as well as the National Institute of Allergy and Infectious Diseases (NIAID), it poses a threat of bioterrorism (Mohapatra et al. 2024). The fruit bat (*Pteropus medius*) is a reservoir host of NiV and is responsible for animal-to-human transmission (Hayman et al. 2008). The first known case of NiV was documented in 1998 in the Malaysian town of Sungai Nipah, followed by cases in Bangladesh, India, Singapore, and the Philippines. Infections were reported to have occurred in humans from pigs, the virus's intermediate host. Since 1999, there have not been any recorded NiV outbreaks in Malaysia. Nevertheless, in India and Bangladesh, new cases have been reported quite regularly (Chadha et al. 2006; Blum et al. 2009). Between 2001 and 2015, several NiV encephalitis cases in Bangladesh have been documented. In 2018, a NiV epidemic was reported from Kerala, India (Kozhikode district), and it was later confirmed that the index patient had contracted the virus from fruit bats (Thomas et al. 2019). However, there were no clinical or statistical data to support the transmission. Because of the high human mortality rate of NiV, zoonotic origin, the likelihood of inter-human contagion, and unavailability of a vaccine, NiV has been declared a global epidemic. The World Health Organization (WHO) has designated it as a worldwide epidemic-causing pathogenic agent, and NiV infection is deemed to be one of the most severe health concerns (Anderson et al. 2019). While only ~ 10% of Nipah-infected individuals contribute to viral transmission, the spread of the disease is considered to be highly heterogeneous and may infect several people (Nikolay et al. 2019). Recently, in 2019, NiV infection was reported from the Ernakulum district of Kerala, India (Sudeep et al. 2021). Another incidence of NiV encephalitis was reported on September 5, 2021, with the demise of a 12-year-old boy, due to this virus, in Kerala's Kozhikode. All these outbreaks have reported high mortality rates, including a ~ 91% mortality rate reported for the recent Kerala outbreak (Arunkumar et al. 2019a). According to a report from Aster MIMS Hospital in Calicut, India, the most recently recorded emergence of NiV occurred in the Malappuram town in Kerela on 21 July 2024, where a 14-year-old boy died from NiV infection, and another 60 individuals were put in the high-risk category. A detailed information about the CFR and geographical outbreaks of NiV since 1998 is depicted in Figs. 1, 2, and 3.

To date, no dedicated antivirals or vaccines have been successfully developed for treating or preventing NiV, and only symptomatic management treatments are given to patients. This emerging zoonotically transmitted virus might cause a global health issue and thus require a universal approach to reduce its disease burden. As NiV is considered a BSL- 4 pathogen, scientists have speculated that it has the capacity to trigger a future pandemic. Hence, there is an urgent need to conduct rigorous research, in order to develop vaccines and therapies against NiV.

In this review, we have discussed the genetic composition, epidemiology, diversity, pathology, prophylaxis, clinical aspects, and the risk factors associated with NiV. This review encompasses the collective data published up to July 1, 2024, in the form of research articles, literature reviews, and case reports. This review also focuses on different circulating NiV strains and provides a comparative analysis of these strains based on their origin, lethality, and mode of transmission from reservoir to host species. Additionally, this review also includes clinical data obtained from various model organisms used to study the biology of NiV. Furthermore, this review discusses presently available and ongoing medical countermeasures against NiV in accordance with the epidemiological data provided by the Coalition for Epidemic Preparedness Innovations (CEPI), WHO, and other public health organizations.

Genetic diversity associated with NiV strains

NiV was first isolated in 1999 (Farrar 1999) and currently two major genetic lineages of human disease-causing NiVs have been identified by genome sequencing, i.e., NiV Bangladesh (NiV-B) and NiV Malaysia (NiV-M) (Harcourt et al. 2005) (Table 1). Both lineages have similar lengths of nucleotides except for an extra six nucleotides located at the 5′ non-translated region of the F protein of NiV-B (Chan et al. 2001; AbuBakar et al. 2004). Although both strains have high sequence identity (91.8%), NiV-B is proposed to have greater mortality rate (Lo et al. 2012). Moreover, the NiV strains isolated from India showed 99% and 97% resemblance to the Bangladeshi lineage (Pallivalappil et al. 2020).

However, in the clinical course, several differences have been reported between NiV-B and NiV-M epidemics. In contrast to NiV-M, NiV-B has a narrower average incubation period (Kulkarni et al. 2013). Although genetically comparable, NiV strains from Bangladesh and India caused a much larger number of deaths in comparison to the NiV-M strain, though that was largely due to the poor quality of health services and the high frequency of new viral infections in these countries (Sharma et al. 2019; Ochani et al. 2019; Thakur

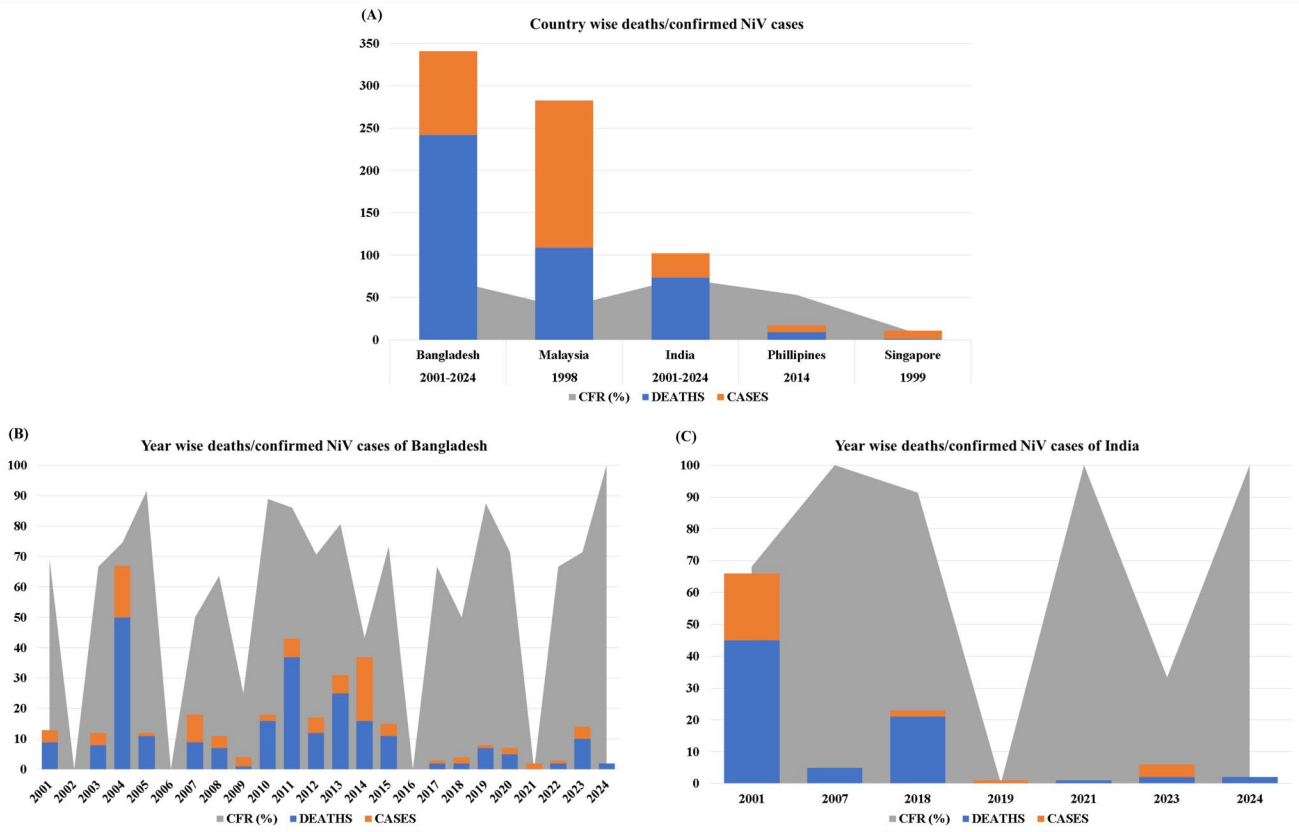

Fig. 1 Epidemiological trends of Nipah virus (NiV) outbreaks illustrating confirmed cases (orange), deaths (blue), and case fatality rates (CFR) (grey). **A** Country-wise distribution of NiV cases and deaths, with the CFR demonstrating variability in virus infectivity across nations. **B** Year-wise trends in Bangladesh, highlighting recurrent outbreaks since 2001, with variations in case numbers and CFR over the years. **C** Year-wise deaths over confirmed cases data for India, emphasizing notable outbreaks in Kerala (2001, 2018, and 2023), where CFR has remained high despite improved surveillance and healthcare responses. The graphs combinedly demonstrate the impact of NiV, showing global as well as regional differences in epidemiological dynamics and disease outcomes

and Bailey 2019). The NiV-B infections are generally associated with both respiratory illness and encephalitis. However, NiV-M infections are primarily associated with encephalitis, with limited evidence of respiratory disease (Chadha et al. 2006; Hossain et al. 2008). NiV-B strain is more frequently linked to the development of atypical pneumonia with respiratory distress. Inter-human transmission cases with the absence of involvement of intermediary hosts were more frequently reported in the NiV-B strain, which has a high mortality rate of ~ 75% compared to the ~ 40% mortality rate of the NiV-M strain (Fig. 1) (Mire et al. 2016). At the same time, the genetic heterogeneity within NiV-B strains is considerably higher compared to the NiV-M strain.

Although NiV-B has shown associations with multiple outbreaks, all in vitro and in vivo therapeutic studies have been focused on the NiV-M strain instead of the ubiquitous NiV-B strain (Clayton et al. 2012). The two strains are biologically indistinguishable, various investigations performed using both small animal models like hamsters, and ferrets and large animal models like African green monkeys (AGMs) indicate that the two strains are distinct in several ways (Baseler et al. 2015). Disease pathogenesis and cytopathic effects were lower in NiV-B-infected hamsters relative to NiV-M-infected hamsters (DeBuysscher et al. 2013). Similarly, it has been shown that disease progression and development of immune responses were slower in NiV-B infections as compared to NiV-M. These findings were further confirmed, by the viral replication titer studies that showed that viral replication was slower during NiV-M infection. However, NiV-B and NiV-M strains caused similar lesions in the hamster's respiratory tract, indicating that there are no inherent differences between the two strains causing human epidemics (Baseler et al. 2015). NiV-B and NiV-M infections in ferrets resulted in similar pathological phenotypes and diseases. Ferrets with NiV-B or NiV-M infection have a much higher viral load in their blood, and ferrets with NiV-B infection have a higher shedding rate in their oral secretions, leading to higher transmission rates of NiV-B, between humans, during outbreaks (Clayton et al. 2012). In AGMs, NiV-M infection caused 50% mortality,

Fig. 2 Global distribution of Nipah virus (NiV) outbreaks, highlighting cumulative deaths over confirmed cases. The map illustrates affected countries, including Malaysia, Bangladesh, India, Singapore, and the Philippines, with outbreak hotspots marked according to the reported number of cases and fatalities. The color intensity represents the severity of outbreaks, with the highest number of cases recorded to date. Regions with repeated outbreaks in India (Kerala and West Bengal) have been highlighted in blue

whereas NiV-B infection resulted in the death of all the experimental animals (Mire et al. 2016).

Host range

Fruit bats, predominantly belonging to the genus *Pteropus* act as reservoir hosts for NiV. In Malaysia, NiV has been detected in different bat species like *Pteropus vampyru*, *Pteropus hypomelanus*, and *Pteropus lylei* (Yob et al. 2001; Wacharapluesadee et al. 2005). In India, NiV was first identified in *Megaderma spasma* and later detected in fruit bats such as *Pteropus giganteus* (Yadav et al. 2012). Investigations into the Malaysian outbreak revealed that pigs can act as both intermediate and amplifying hosts for this virus (Mohd Nor et al. 2000; de Wit and Munster 2015). Serological studies confirmed NiV infection in dogs, at the time of Malaysia's first outbreak, and viral transmission was associated with the ingestion of virus-infected pork or direct physical contact with NiV-infected pigs (Mills et al. 2009). A 2001 study reported the spread of NiV from sick cows in the Meherpur district of Bangladesh (Hsu et al. 2004). Domestic animals, namely cows and goats, are an important factor in the spillover of bat-borne viruses like NiV, although their exact roles as amplifying or bridging species are not yet completely known (Chua 2003; Glennon et al. 2018) (Fig. 4).

Mode of transmission and risk factors

Humans mainly contract NiV via foods contaminated by infected bats, proximity to infected animals, and body fluids from infected individuals (R et al. 2008; Luby et al. 2009). Virus spread from bats to pigs is attributed to the ingestion of leftovers or fruits contaminated by NiV-infected bats (Luby 2013). Bat infections can be transmitted to humans in primarily two ways (Fig. 4): through an intermediary animal host (outbreak in Malaysia), or straight from bats to humans (outbreaks in Bangladesh and India) (Hsu et al. 2004). In the case of the Malaysian outbreak, the major risk of human-to-human NiV transmission was linked to direct exposure to the infectious secretions or excretions of NiV-infected pigs which happened mainly during the handling of pigs (Luby and Gurley 2012). Alarmingly, the transport of pig meat from NiV-infected areas to other geographical locations worldwide may have also facilitated the transmission of the disease to uninfected regions (Kulkarni et al. 2013). This

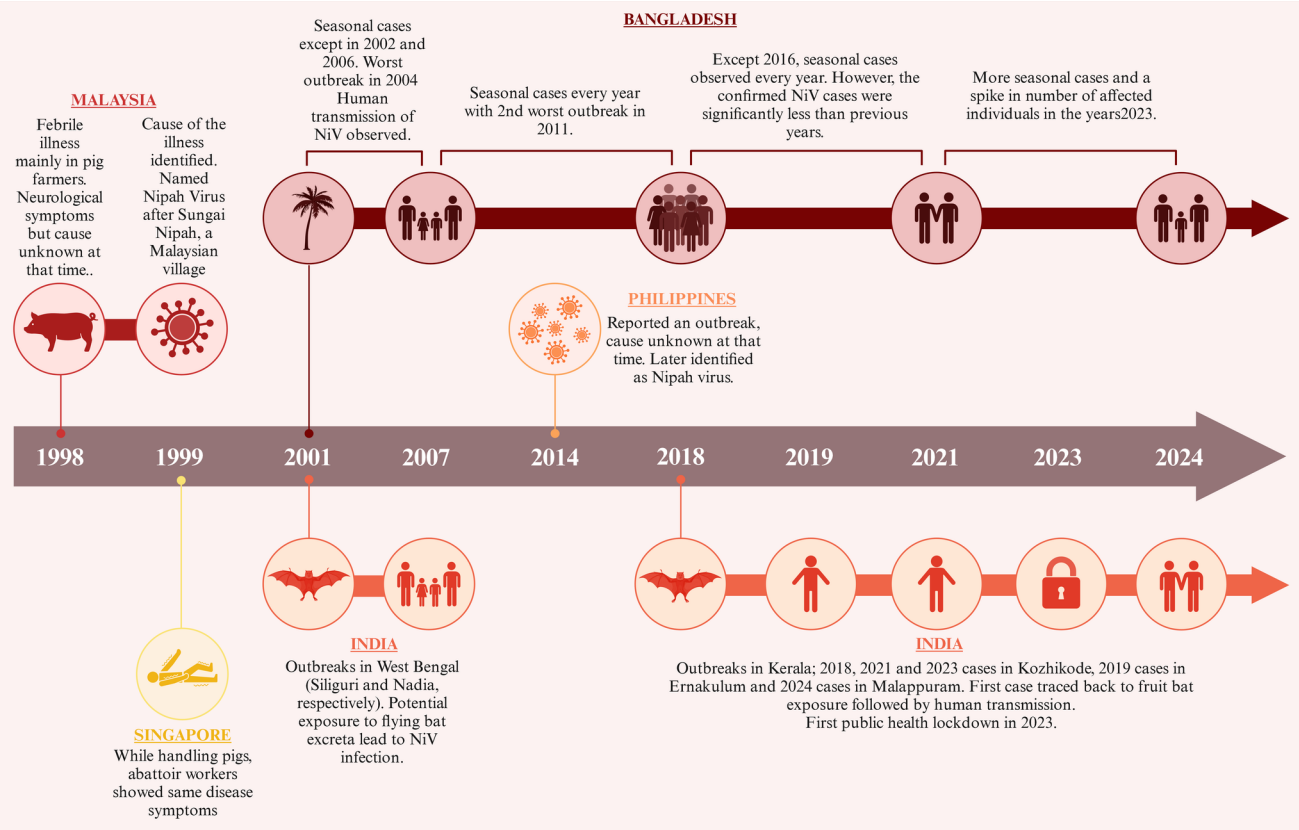

Fig. 3 Timeline of Nipah virus (NiV) outbreaks from 1998 to 2024. The figure illustrates key outbreaks, highlighting their geographic locations, case fatality rates, and major transmission routes. The first recorded outbreak in Malaysia (1998–1999) involved pig-to-human transmission, whereas subsequent outbreaks, particularly in Bangladesh and India, were linked to direct bat-to-human or human-to-human transmission. Notable events include the recurrent outbreaks in Bangladesh since 2001, the Kerala outbreaks in India (2018, 2019, and 2023), and recent cases in 2024

was evident in Singapore, where the import of infected pork from Malaysia led to the spread of NiV infection among abattoir workers (Chew et al. 2000). In Bangladesh, ingesting infected date palm sap was a common risk factor associated with human NiV infections (Chakraborty et al. 2016). Working in a healthcare setting increases the risk of being vulnerable to NiV infection, mainly because of the sneezing and coughing of infected individuals, resulting in the formation of aerosol droplets containing infectious viruses, which infect other individuals in poorly ventilated rooms (Wang et al. 2021). A recent study, undertaken on Syrian hamsters, using aerosolized NiV suggested that the transmission of NiV occurred through aerosolized NiV droplets, during close contact with animals (Escaffre et al. 2018). Contact with respiratory and urine secretions from infected individuals is another cause of human-to-human spread (Gurley et al. 2007). Research carried out in Bangladesh by Hassan et al. revealed that hospital surfaces, like the area of the wall in contact with patients, bed sheets, and patient record files, were contaminated with NiV RNA (Hassan et al. 2018). A significant outbreak in India stemmed from nosocomial transmission via respiratory secretions, primarily owing to inefficient utilization of personal protective equipment (Chadha et al. 2006). Individuals having direct physical contact with NiV-infected patients but had not come into direct contact with their body fluids had a reduced probability of developing subclinical illnesses (Gurley et al. 2007). NiV-infected patients with hard breathing are more likely to spread the virus, than those without any respiratory issues (Luby et al. 2009).

Animal models used for studying NiV

The availability of animal models is a critical factor for understanding the pathogenesis of viral diseases. Several animal models exist for studying NiV viz bats, cats, dogs, ferrets, horses, African green monkeys (AGM), squirrel monkeys, pigs, mice, immunodeficient mice, hamsters, guinea pigs, rats, rabbits, and chickens. Guinea pigs were among the first to be used in animal experiments to study NiV. They were subjected to both intranasal and

Table 1 Comparative analysis of NiV strains—NiV-Malaysia (NiVM), NiV-Bangladesh (NiVB), and NiV-India (NiVI)—based on key epidemiological, clinical, and virological characteristics. It highlights differences in mortality, human-to-human transmission rates, clinical manifestations, and public health responses

Feature	NiV-Malaysia (NiVM)	NiV-Bangladesh (NiVB)	NiV-India (NiVI)
First identified	1998–1999 (Malaysia and Singapore)	2001 (Bangladesh)	2001 (India, Siliguri outbreak)
Primary reservoir	Pteropus fruit bats	Pteropus fruit bats	Pteropus fruit bats
Intermediate host	Pigs; Horse (Philippines)	None (direct bat-to-human transmission)	None (direct bat-to-human transmission)
Major outbreaks	Malaysia (1998–1999), Singapore (1999); Philippines (2014)	Bangladesh (2001, 2003, 2004, 2011, 2018)	Siliguri (2001), Kerala (2018, 2019, 2021, 2023)
Mortality rate (%)	~ 40%	65–100%	70–100%
Morbidity (severity of disease)	Severe encephalitis, high case recovery rate	Acute respiratory distress, severe encephalitis	Acute respiratory distress, encephalitis
Human-to-human transmission rate	Low (~ 8%)	High (~ 33–75%)	High (~ 75%)
Mode of transmission	Zoonotic (pig-to-human; horse-to-human) with limited human-to-human	Direct bat-to-human and human-to-human (via saliva, respiratory droplets)	Direct bat-to-human and human-to-human (via saliva, respiratory droplets)
Clinical features	Fever, encephalitis, respiratory involvement rare	Fever, cough, acute respiratory distress, encephalitis	Fever, severe respiratory distress, encephalitis
Unique epidemiological features	Pigs as amplifying hosts, first outbreak outside India/Bangladesh, led to culling of > 1 million pigs	Frequent spillovers, seasonal outbreaks (winter-spring), human-to-human super-spreader events	Recurring outbreaks in Kerala, high human-to-human transmission, limited genetic data available
Genetic differences	More closely related to Hendra virus (HeV)	More virulent, higher human-to-human spread	Closely related to NiVB but with distinct mutations
Public health response	Culling of pigs, quarantine measures, strict biosecurity protocols	Case isolation, community awareness, surveillance	Case isolation, contact tracing, state-wide lockdowns during outbreaks

intraperitoneal inoculation with NiV; however, the former failed to elicit any clinical symptoms and, hence, the peritoneal route was considered more suitable for administering NiV inoculum (Middleton et al. 2007). Pigs infected through oral routes showed symptoms of natural NiV infection but increased severity was observed after subcutaneous inoculation of NiV (Middleton et al. 2002; Weingartl et al. 2005). Subcutaneous, intranasal, or oral routes of infection in cats showed clinical symptoms within 4–8 days (Mungall et al. 2006). Every method of inoculation leads to infection or death, with the virus being detected across several organs such as the brain, kidney, spleen, and lungs (Hooper et al. 2001). Cats developed good IgG and IgA responses in vaccine studies when challenged with a 50,000 $TCID_{50}$ dose of NiV (Zhu et al. 2006; McEachern et al. 2008). In pregnant cats, NiV was found in the fetal tissue, placenta, and uterine fluid, and they were involved in the vertical transmission of NiV (Mungall et al. 2007). Ferrets also served as animal models and were widely used to check the efficacy of antivirals and vaccines against henipaviral infection (Bossart et al. 2009; Clayton et al. 2016; Mire et al. 2020). Ferrets subjected to NiV infection developed respiratory and neurological symptoms including fever, cough, nasal discharge, depression, and paralysis (Bossart et al. 2009; Pallister et al. 2009, 2011).

Both AGMs and squirrel monkeys are extremely vulnerable to NiV infection and exhibit common clinical symptoms that are also observed in human NiV cases (Marianneau et al. 2010; Geisbert et al. 2010, 2020). Experimental infection of AGMs revealed that the NiV-B strain exhibited increased pathogenicity as compared to NiV-M (Mire et al. 2016; Prasad et al. 2020) Due to their high genetic similarity with humans, AGM models have been extensively used for testing antiviral drugs against NiV (Rockx et al. 2010; Bossart et al. 2011, 2012). Common laboratory mice models like Balb/c and C57BL/6 did not develop henipaviral infection post-exposure to the virus via intra-nasal or intraperitoneal route; however, intracranial administration of the virus caused fatal infection (Westbury et al. 1995; Dhondt et al. 2013). Despite having a lower susceptibility to NiV infection, murine models are widely employed to assess the efficacy of mRNA vaccine candidates (Valbuena et al. 2014; Yun et al. 2015; Keshwara et al. 2019; Stroh et al. 2019; Kalodimou et al. 2019; Shuai et al. 2020; Li et al. 2020; Loomis et al. 2021). Golden Syrian hamsters are another in vivo animal model for testing henipaviral therapeutics,

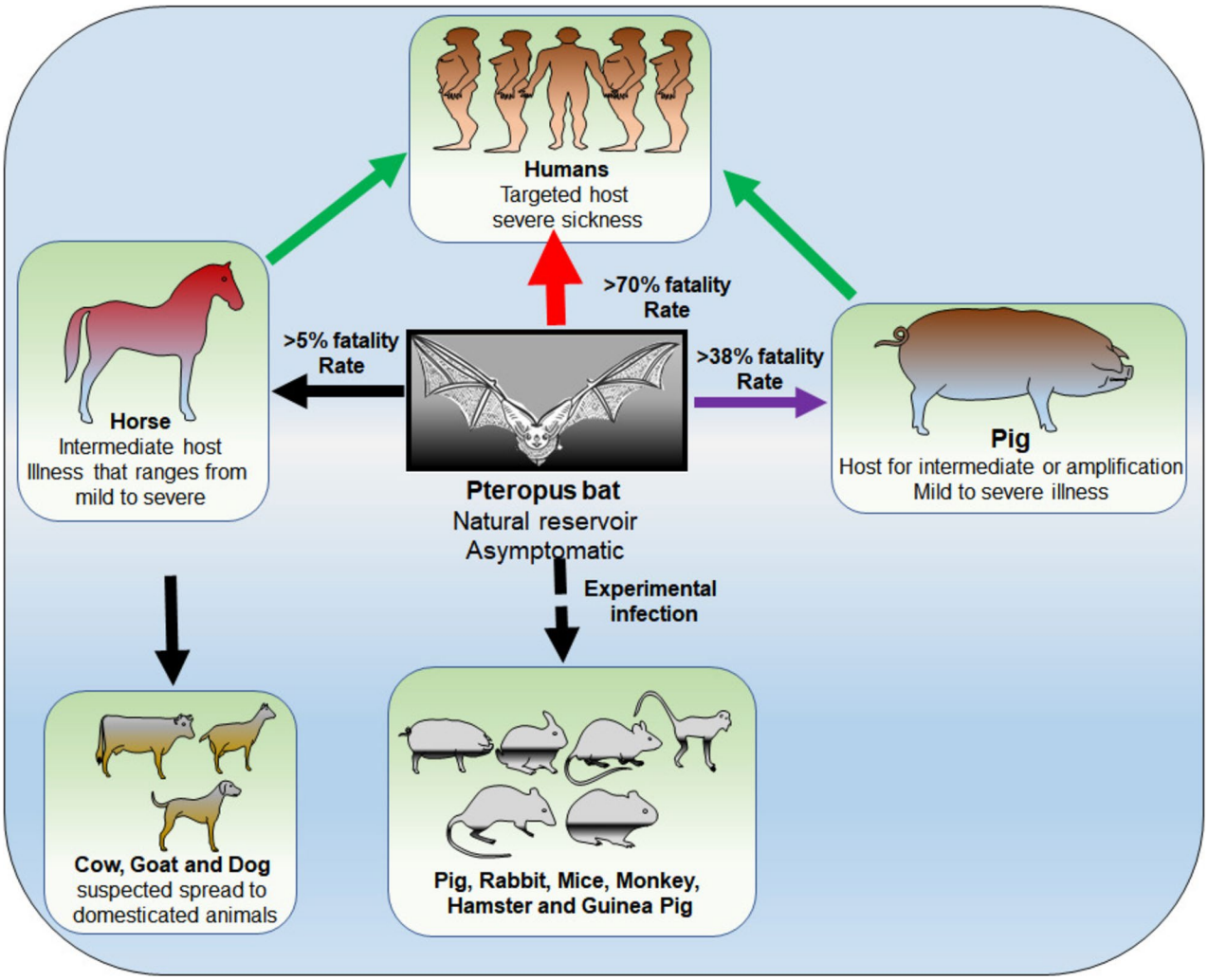

Fig. 4 Illustration of the complex dynamics of Nipah virus transmission in various animal models. The intricate interactions involved in the virus's transmission among different species are graphically depicted

as they recapitulate similar pathological manifestations as those in humans (Guillaume et al. 2004a; De Wit et al. 2011; Marsh et al. 2012; Baseler et al. 2016; Escaffre et al. 2018). Intranasal or intraperitoneal inoculation of NiV on hamsters showed clinical signs of infection in the respiratory and nervous systems (Wong et al. 2003).

Genome of NiV

NiV is a pleomorphic, thread-like, or spherical, encapsulated virus that ranges in size from 40 to 1900 nm with a single layer of surface projections that are ~ 17 nm in length (Ang et al. 2018; Singh et al. 2019). It has a negative-sense, single-stranded, non-segmented, RNA genome of ~ 18.2 kb (Jack et al. 2005). RNA viruses have a higher potential of infecting new host species, due to their incredibly short generation time, and their ability to evolve faster, due to high mutational frequency. They are currently thought to be the key etiological agents for ~ 25–44% of current infectious illnesses (J Woolhouse et al. 2013; Devnath and Masud 2021).

The NiV genome codes for six structural proteins, namely, fusion protein (F), attachment glycoprotein (G), matrix protein (M), phosphoprotein (P), nucleoprotein (N), and the large RNA-dependent RNA polymerase protein (L). Further, the P gene codes for three non-structural proteins that include proteins C, W, and V (Fig. 5) (Sun et al. 2018). The N, P, and L proteins, in conjunction with the viral RNA, form the virus ribonucleoprotein (vRNP) complex, that regulates transcription of the viral genome and viral replication (Ranadheera et al. 2018) The NiV F protein is heavily glycosylated and mediates viral entry and integration into the host membrane (Aguilar et al. 2006). Studies have confirmed that altering the glycosylation pattern in F protein diminishes its fusion

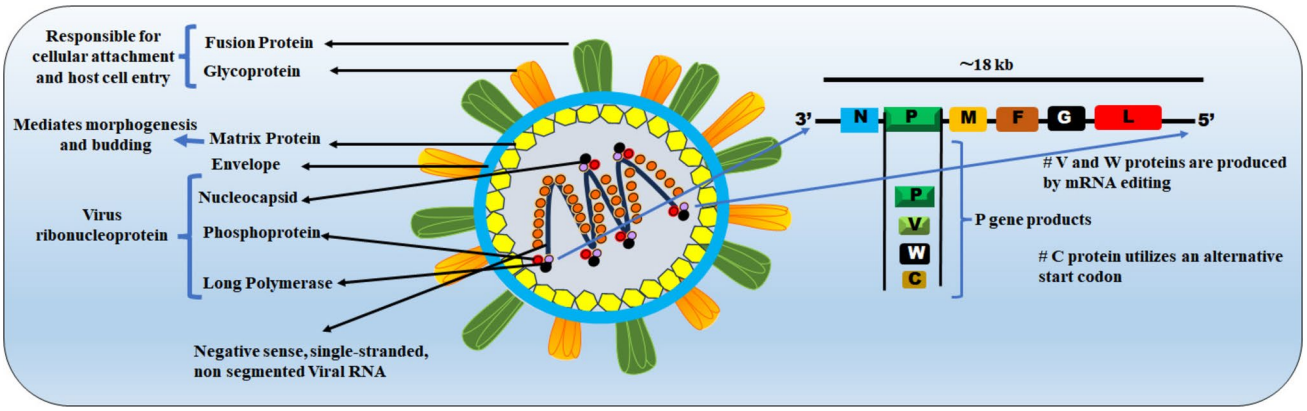

Fig. 5 Representation of the structure and proteins of the Nipah virus. Comprehensive illustration of the virus's molecular structure provides an unobstructed view of its structural elements. All the important structural elements and proteins of the Nipah virus are shown

efficacy. At the same time, different investigations have reported that the N-glycans on NiV G glycoprotein act as a decoy and protect the viral envelope from antibody-mediated neutralization (Biering et al. 2012; Aguilar et al. 2006). The NiV-F glycoprotein in its pre-fusion form is a hexamer of trimers for which the crystal structure has already been determined (Xu et al. 2015), while NiV-G glycoprotein is a homo-tetramer whose crystal structure has also been solved (Bowden et al. 2008). The F and G proteins, along with three accessory proteins (C, W, and V), encapsulate the NiV viral genome (Fig. 5) (Rodriguez et al. 2002, 2004; Shaw et al. 2004). The NiV-F and NiV-G proteins are major targets of neutralizing antibodies as they help in not only viral binding and fusion but also viral budding (Vogt et al. 2005).

Pathogenesis of NiV

Virus entry

The oronasopharyngeal route serves as the primary passage through which NiV enters the host, and studies involving infected pigs and hamsters have confirmed respiratory epithelium to be the first site of NiV infection (Weingartl et al. 2009; De Wit et al. 2011). Following initial replication in the respiratory tract, NiV spreads systemically, infecting airway endothelial cells during viremia and subsequently targeting epithelial cells in the bladder and kidneys (Lamp et al. 2013). With disease progression, NiV enters the bloodstream and infects the brain, digestive, and excretory systems (Talukdar et al. 2023). Entry of NiV inside the CNS can happen due to multiple reasons such as replication of NiV in the endothelial cells resulting in the compromised integrity of the blood–brain barrier (BBB); the transmigration of NiV-bound uninfected leukocytes into the brain; and the transport of NiV through the nasal cavity into the CNS via olfactory neurons (Weingartl et al. 2005; de Wit and Munster 2015). Nucleoprotein aggregation in degenerating axons is an effective mechanism for NiV dissemination throughout the CNS, following its entrance into most animal models (Munster et al. 2012).

Host–pathogen interactions

The F and G proteins present in the viral envelope of NiV control virus attachment and its entry into host cells (Figs. 6). Ephrin-B2 (EFNB2) and ephrin-B3 (EFNB3), which are host cell receptors, found on epithelial cells and neurons, respectively, serve as a binding partner for the G protein. Seven contiguous residues on top of the globular head of G protein mediate its interaction with the EFNB2 receptor (Guillaume et al. 2006). The interlinkage of the receptor exposes the G protein's stalk domain and induces F protein conformational changes, from pre-fusion form to pre-hairpin intermediate, and finally to post-fusion form that is ready for membrane fusion (Ortega et al. 2022). The presence of a KKR motif located in the cytoplasmic tail of the F protein stimulates viral membrane fusion with the host cells in a pH-independent manner, thereby allowing virion penetration (Lamp et al. 2013; Aguilar et al. 2007; Negrete et al. 2005; Xu et al. 2012) (Fig. 6). The F protein is initially present as a precursor, F_0, which undergoes proteolytic processing. This processing is likely mediated by cathepsin L in Vero cells, and cathepsin B in MDCK cells, resulting in the formation of disulfide-linked F_1 and F_2 subunits that constitute a mature fusogenic F heterodimer (Pager et al. 2006; Diederich et al. 2012). The F_1 subunit mainly facilitates the fusion of the viral membrane and the host cellular membrane.

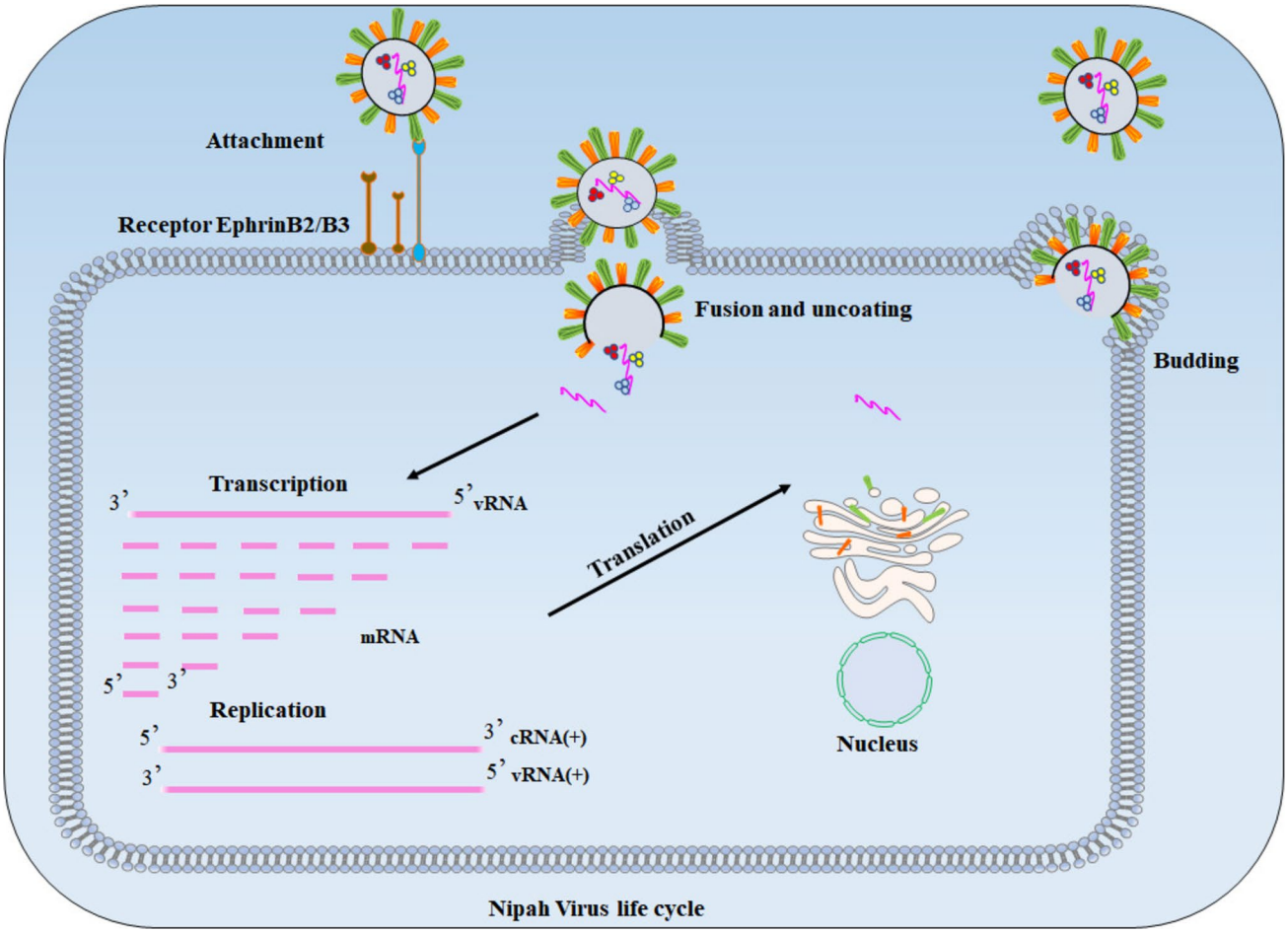

Fig. 6 Representation of the Nipah virus life cycle, including all important phases from entry to exit in host cells. Graphical illustrations of how the virus enters the cell, replicates, and leaves the cell are shown

Cellular mechanisms, viral replication and budding

The binding of the G protein with the ephrin-B2/B3 receptor, followed by viral entry, triggers the release and duplication of the viral mRNA of NiV (Fig. 6) (Bonaparte et al. 2005). Subsequently, the viral mRNA undergoes translation into the primary structural proteins, after the L and P proteins mediate its transcription (Patch et al. 2007). The molecular weight of NiV L protein is ~ 250 kDa and is responsible for replication, transcription, and capping of the viral genome, in close coordination with the viral phosphoprotein P. The L protein's C-terminal region contains an RNA-dependent RNA polymerase (RdRp) domain; a poly-ribonucleotidyltransferase (PRNTase) domain essential for mRNA capping; a methyltransferase (MTase) domain; and an uncharacterized domain (Diederich and Maisner 2007; Cox and Plemper 2017). The N protein also participates in replication, gene transcription, and wrapping of the viral genome (Lo et al. 2012).

The molecular features of the virus are preserved by the M protein, as it recruits a variety of cell machinery, to initiate viral morphogenesis and virion budding (Watkinson and Lee 2016; Eaton et al. 2006). The M protein also participates in the last phase of the assembly of the virion, which includes virion encapsulation, followed by the release of new virus particles from the host cell (Sun et al. 2018). Furthermore, the M protein acts as a shuttle between the nucleus and cytoplasm, as it contains nuclear import/export signal sequences, and performs nuclear transit, even though NiV replicates in the cytoplasm (Ringel et al. 2020). Inhibition of the nucleolar treacle protein by virus-mediated modulation of the host cell machinery enhances Henipavirus production as this targets the DNA-damage response (DDR) pathway (de Wit et al. 2014; Rawlinson et al. 2018). Aggregation of M protein leads to the formation of virus-like particles (VLPs) at the plasma membrane and in association with the F protein it induces G protein recruitment into VLPs (Johnston et al. 2017; Sun et al. 2018).

Host immune response

In vitro studies, involving endothelial cell lines, infected with NiV, have been found to trigger the release of type I interferon (IFN-I), and various cytokines and inflammatory chemokines (Lo et al. 2010). Upon NiV attachment and subsequent fusion with host cells, RNA helicases present in the cytoplasm recognize viral RNA, inducing a strong IFN-I response that causes the activation of multiple IFN-induced genes, like OAS1, ISG56, and IP- 10, thereby influencing innate antiviral defense (Habjan et al. 2008; Leon et al. 2018). A constitutive INF level is maintained by pteropid bats even in the absence of infection, which helps them to inhibit NiV replication, and act as a reservoir without getting infected (Liew et al. 2022). In in vivo studies, involving NiV-infected Syrian Golden hamster, the upregulation of IFN-I signaling, cytokines, and chemokines initially occurred in the lung, followed by the brain, correlating with disease progression (Rockx et al. 2011). Apart from IFN-I response, pro-inflammatory cytokines, such as IL- 1 and TNF-α, were also induced, following NiV infection (Liew et al. 2022).

Serum samples, from NiV-infected survivors, of the 2018 Indian outbreak, displayed elevated B-lymphocyte counts, correlating with the production of anti-NiV IgG and IgM antibodies (Arunkumar et al. 2019b). However, the adaptive immune response against NiV is not completely clear in humans due to insufficient clinical samples from fatal cases. Studies, involving animal models, were conducted to have a better understanding of NiV-induced humoral responses. Swine subjects, experimentally infected with NiV, developed neutralizing antibodies that became detectable within a week and reached high titers by 2 weeks post-infection (Berhane et al. 2008). On the other hand, African green monkeys exhibited B cell exhaustion by 12 days post-NiV infection, which indicated rapid progression of infection (Lara et al. 2019).

Immune evasion strategies

Detection of viral RNA, by receptors like RIG-I and MDA-5, induces the production of IFN-β which triggers the JAK/STAT pathway and downstream signaling pathways that regulate IFN-stimulated gene expression (García-Sastre and Biron 2006). It has been seen in various studies that the NiV P, V, W, and C proteins help to bypass the defenses imposed by the host immune system. To inhibit JAK/STAT signaling, the W, V, and P proteins of NiV bind to STAT1 protein, through their N-terminal domain, and stop it from getting phosphorylated (Shaw et al. 2004). MDA- 5 and RIG-I, as well as STAT2, which is another contributor to antiviral responses, are inhibited by the phosphatase PP1 mechanism of NiV V protein. Both NiV V and W proteins are responsible for blocking IKKε signaling, which affects signaling pathways induced by viral RNA or TLR3. The C protein blocks IFN-α induction and indirectly suppresses type I IFN induction, by reducing the synthesis of viral RNA (Satterfield et al. 2016b).

Tissue tropism

In humans, NiV causes a severe and fast-developing disease, mostly affecting the respiratory and central nervous systems (CNS) (Hossain et al. 2008). More than 90% of infections impact the CNS and 62% of infections affect the respiratory system. Biopsy samples taken from NiV-infected individuals' brains and other body organs revealed the presence of syncytial multinucleated large endothelial cells that distinguish NiV-associated encephalitis, from encephalitis caused by other viruses (Wong et al. 2002; Weingartl et al. 2005). Endothelial cells, macrophages, neurons, glial cells, smooth muscle cells, alveolar pneumocystis cells, and epithelial cells in the upper respiratory tract are among the many cell types that NiV may infect (Moldoveanu et al. 2009). The ephrin-B2/B3 receptors play an important role in determining the virus's ability to infect cells. A study conducted on NiV-infected Syrian hamsters reported that NiV antigens were absent in veins, but present in medium- and small-sized arteries. These findings align with the fact that the ephrin-B2 receptor is expressed in the arterial endothelium, but absent in venous endothelium (Bossart et al. 2008). Although NiV receptors are abundantly accessible, the virus must spread throughout the body, via bloodstream to reach and infect various cell types (Mathieu et al. 2011).

Once NiV enters the bloodstream, it disseminates to the spleen, brain, and kidneys, either in free-form or in a host leukocyte-bound form (Rockx et al. 2011; Escaffre et al. 2013). The tropism of NiV, into the capillaries of the brain and lungs, is mediated by infection of CD6-expressing T cells, which acts as a ligand for the CD166 molecule (activated leukocyte cell adhesion molecule (ALCAM)), displayed by microvascular endothelial cells present in the blood–brain and blood-air barrier (Erbar et al. 2008; Stachowiak and Weingartl 2012). Disruption of the BBB is followed by infection of the CNS by the virus. This results in the production of TNF-α and IL- 1, which in turn triggers the onset of neurological symptoms. In lungs, type 2 pneumocytes and bronchial epithelium serve as the principal targets of these antigens (Rockx et al. 2011). Infection of the airway epithelium activates inflammatory mediators (Escaffre et al. 2016), and in the latter stages of the illness, the virus spreads to the lung endothelial cells (Baseler et al. 2016). Inflammation of the respiratory tract epithelium causes acute respiratory distress syndrome (ARDS)–like condition, which subsequently triggers the production of inflammatory cytokines (Moldoveanu et al. 2009). In addition to leukocytes, other immune cells such as T lymphocytes, NK cells,

and monocytes can also be infected by NiV (Stachowiak and Weingartl 2012).

Clinical features linked with NiV

The incubation time for NiV has been reported to be less than 15 days (Hossain et al. 2008). However, in certain situations, the incubation period may go up to 4 months or more (Goh et al. 2000). It has been noted that latent infection might resurface, after several months/years, post-acute infection (Ang et al. 2018). Asymptomatic infections are very unlikely in cases with NiV infections (Parashar et al. 2000). Patients generally begin to show symptoms of infection after 3 to 14 days of exposure to NiV (Hossain et al. 2008; Arunkumar et al. 2019). The body temperature rises quickly, causing lethargy and a headache and certain individuals may exhibit coughing and respiratory discomfort at the same time (Hossain et al. 2008). A sore throat, nausea, and muscular pain are all possible symptoms associated with NiV infection (Singh et al. 2019). Within 24–48 h of infection, encephalitis may develop, resulting in convulsions and coma in the most severe instances (Benmimoun et al. 1982). The most typical symptoms are hypotonia, gaze palsy, segmental myoclonus, disturbed mental state, and areflexia, as well as weakness in the limbs (Chua et al. 2001). Additionally, several clinical characteristics are also associated with vascular and cell injuries in the brain, lungs, and kidneys (Wong et al. 2002). Patients go from stable to comatose in a matter of days and about 20% of survivors develop residual neurological abnormalities, which include tiredness, localized neurological problems, and depression (Montgomery et al. 2008). Septicemia, renal failure, and gastrointestinal bleeding are the other possible side effects of this infection (Wong et al. 2002). In addition to these symptoms, histopathological investigations revealed meningitis, interstitial pneumonia, and pulmonary edema in several studies (Parashar et al. 2000; Field et al. 2001; Mills et al. 2009).

Laboratory Diagnosis

An early diagnosis is extremely critical for NiV infection, because NiV infection is characterized by serious case fatalities. For clinical diagnosis, blood, throat/nasal swabs, urine, and cerebrospinal fluid from infected people and animals are used as samples. Virological diagnosis involves detecting viral RNA, through nucleic acid amplification tests (NAATs), for instance, reverse transcriptase-polymerase chain reaction (RT-PCR), which offer high sensitivity and specificity, particularly during early infection stages. Immunohistochemistry and virus isolation techniques are also employed for confirmatory diagnosis, although virus isolation is more time-consuming (Mazzola and Kelly-Cirino 2019; Pandey et al. 2024). Serological assays, like enzyme-linked immunosorbent assays (ELISA), detect NiV-specific IgM and IgG antibodies. Apart from these, polymerase chain reaction (PCR) and recombinase polymerase assay have also been used to detect NiV (Fig. 7).

ELISA test

ELISA employs a monoclonal antibody (mAb)–based diagnostic approach for NiV detection (Abdullah and Tan 2014; Satterfield et al. 2016a) (Fig. 7). Since the N protein of NiV is more abundantly expressed during the acute stage of NiV infection, researchers cloned, expressed, and purified the recombinant version of the N protein, and used it in an IgM capture ELISA to analyze human sera. IgM antibodies are among the first to appear during infection, usually detectable within the first 5 days of symptoms, and their levels gradually decline over 2–3 months and eventually disappear (Hassan et al. 2022). At the same time, an indirect IgG ELISA was developed that was capable of testing pig as well as human sera (Yu et al. 2006). Anti-NiV IgM peaks were observed in serum samples post- 9 days of infection and were reported to last for up to 90 days (Fischer et al. 2018). On the other hand, anti-NiV IgG peaks are seen 2 to 4 weeks after the onset of symptoms and can last for several months to years. Thus, IgM ELISA is useful for identifying recent or acute infections, while IgG tests are mostly used in serosurveillance studies, where a positive IgG ELISA test confirms the convalescence stage of infection in recovered patients (Mazzola and Kelly-Cirino 2019).

Polymerase chain reaction

The high sensitivity and specificity of PCR makes it a reliable method to detect viral infection (Fig. 7). RNA of NiV in respiratory secretions, serum, urine, and cerebrospinal fluid can be detected by real-time PCR (qRT-PCR). Apart from that, RT-PCR, duplex, and nested RT-PCR (nRT-PCR) can also be used to detect NiV, with amplicon nucleotide sequencing providing further confirmation (Guillaume et al. 2004b; Wacharapluesadee and Hemachudha 2007). The monitoring of the emerging Henipaviruses, including novel NiV strains, was made possible through TaqMan-based qRT-PCR (Applied Biosystems, USA), which involved the identification of unique sequences present in the NiV N gene (Thakur and Bailey 2019).

The absence of adequate infrastructure, required to set up a PCR testing facility, can limit its usage in some endemic regions. Furthermore, these tests might lose their sensitivity due to genetic mutations, which can lead to the appearance of novel NiV variants, exhibiting variations in the conserved sequences that are used to design probes. Probes are often constructed for highly conserved (mutation-resistant)

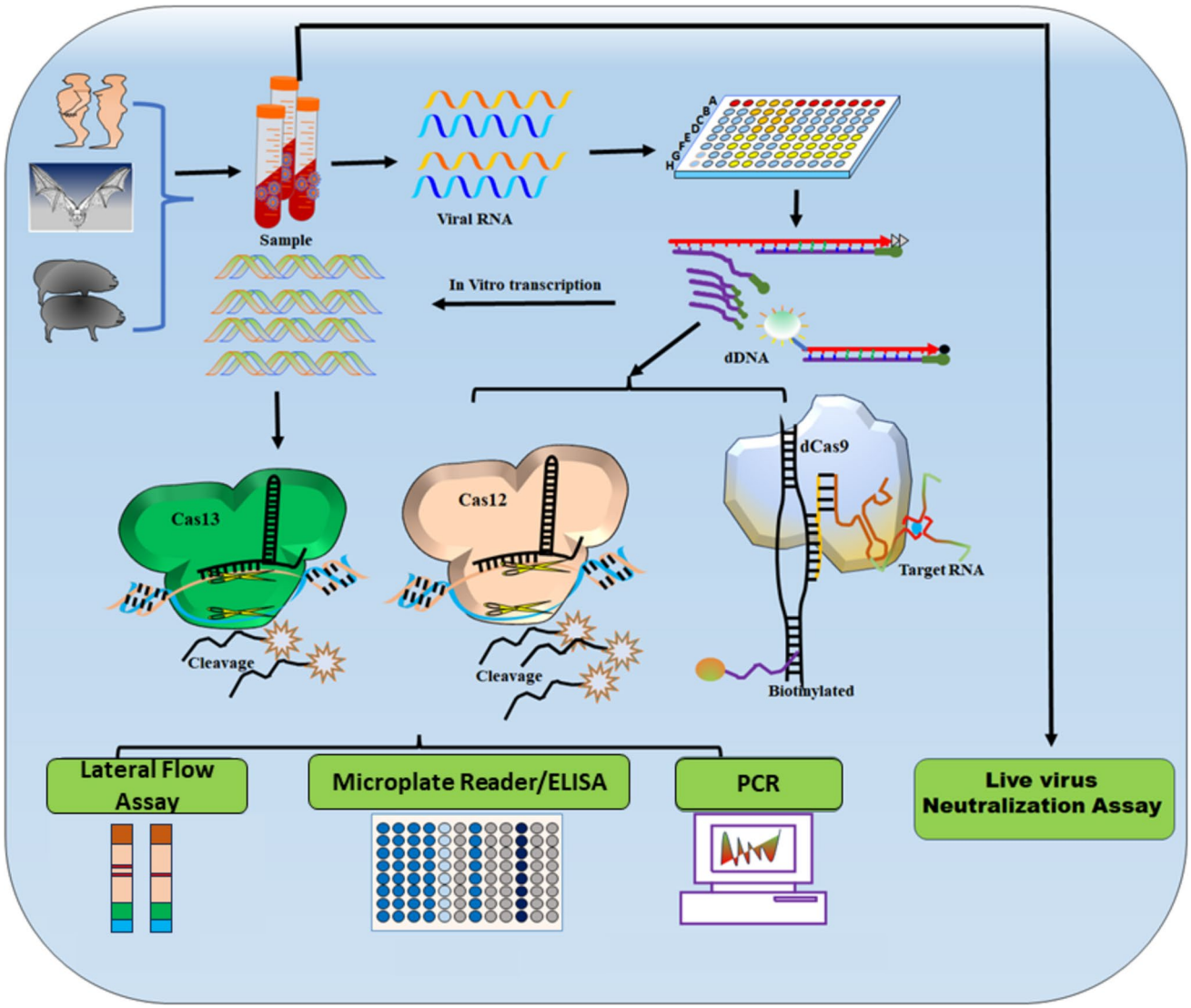

Fig. 7 Illustration of the diagnosis of Nipah virus using a variety of techniques. A variety of virus detection methods and their visual description are shown, e.g., SHERLOCK Assay, Lateral flow assay, ELISA, PCR, and Live Virus Neutralization Assay

regions, present in the sequences of all known strains of the pathogen of interest, to assure coverage for genetic variations. The CDC devised a conventional PCR protocol targeting the NiV N protein (Chua et al. 2000; Lo et al. 2012). RT-PCR assays have targeted the conserved N, M, or P regions of the NiV RNA genome as well. A SYBR Green-based assay encoding primers specific for different regions of N has been additionally reported (Chang et al. 2006), although it has a lesser sensitivity (100 pfu). In 2018, a one-step qRT-PCR was developed, which targets the sequences between the F and G genes, and gives an accurate estimation of replicative NiV RNA (Jensen et al. 2018). This PCR procedure might be more precise than standard qRT-PCR, as it eliminates the mRNA amplification step. A portable, battery-operated PCR machine jointly developed by the National Institute of Virology (NIV), and Molbio Diagnostics Pvt. Ltd., is currently the only approved rapid diagnostic kit available. The effectiveness of this PCR kit called Truenat™ Nipah PoC system was validated by NIV and was found to be ~97% sensitive and ~100% specific. This PCR platform was used during the 2019 NiV outbreak in Kerala and had a detection level similar to the TaqMan rtPCR assay (Yadav et al. 2021; Moore et al. 2024).

Additionally, next-generation sequencing and deep sequencing is an alternate way for effectively identifying viral subtypes and newer strains; however, from a diagnostic perspective, this method is not frequently employed for screening of large number of viral samples (Matranga et al. 2016). It enables a direct sequence analysis of the viral genome, permitting virus as well as lineage determination

without offering information about the virus composition. It enables one to determine the phylogenetic evolution of viral specimens over time and topography, when applied retrospectively (Matranga et al. 2014; Carroll et al. 2015).

Recombinase polymerase amplification (RPA) assay

The incorporation of the CRISPR/Cas technique, in an isothermal amplification assay like RPA, has led to the development of an inexpensive and rapid point-of-care viral diagnostic test called Specific High Sensitivity Enzymatic Reporter UnLOCKing or SHERLOCK. This has been effectively employed to diagnose infections caused by different viruses like Zika, Dengue, Ebola, and SARS-CoV- 2 (Gootenberg et al. 2017; Barnes et al. 2020; Crone et al. 2020; Freije and Sabeti 2021). Recently, in 2024, researchers in China developed a novel diagnostic method that employed the DNase activity of Cas12a protein against the highly conserved N gene of NiV (Fig. 7). Activation of Cas12a, upon target sequence recognition, leads to non-specific cleavage of single-stranded DNA reporters, which is detectable through a microplate reader or on a lateral flow strip (Yang et al. 2024). Similar to this technique, a one-pot RPA-CRISPR assay has also been developed that uses the Cas13a protein and a quenched RNA probe to diagnose NiV (Fig. 7). Unlike the conventional SHERLOCK technique, this one-pot assay reduces the contamination risk and minimizes false-positive results, as the entire assay can be completed in a single tube without the need for reaction transfer (Miao et al. 2023). These novel diagnostic methods offer safer and cost-effective alternatives, as they can be performed in BSL- 2 facilities without requiring expensive thermal cyclers used in conventional PCR assays.

Immunohistochemistry

Immunohistochemistry (IHC) is another way to detect NiV infection which employs formalin-fixed tissue samples (Hooper et al. 1996). Since virus replication occurs in vascular endothelium, tissues can be used from various organs such as the brain, lung, spleen, kidney, and lymph nodes. Initially, IHC was performed using convalescent human serum (Daniels et al. 2001), but currently, rabbit serum against NiV is used (Kashiwazaki et al. 2004). For NiV detection, an antibody-based IHC diagnostic method has been developed by the National Institute of Animal Health in Japan (Tanimura et al. 2004a). The IHC-based detection method involved 4 mice-based mAbs (12 A5, 13 A5, 18 C4 11 F6) that were used to test NiV-infected pig tissue fixed with formalin. The study found that 11 F6 was able to detect NiV antigens across different tissues such as the renal and respiratory epithelium, smooth muscle cells, and at the same time, certain novel tissue sites such as Schwann cells of the spleen, laryngeal epithelial cells, and endothelial cells present in the heart valves were also found to be NiV positive. Apart from that, 12 A5 also showed NiV detection capabilities; however, the binding efficiency of 13 A5 and 18 C4 were reduced. In fatal cases, IHC is used to confirm NiV diagnosis via histopathology (Tanimura et al. 2004b).

Treatment and prophylaxis

NiV is on the priority pathogen list of WHO, as it possesses high pandemic potential and must be taken more seriously. Currently, there are no effective drugs or vaccines targeting NiV, so patient treatment procedures are confined to supportive treatment options and preventative measures only (Sharma et al. 2019; Chakraborty et al. 2019). Maintaining respiratory function, minimizing the likelihood of venous thrombosis, and retaining fluid and electrolyte homeostasis are the most important clinical strategies to combat NiV infection after detection (Aditi and Shariff 2019; Ambat et al. 2019). Furthermore, broad-spectrum antibiotics are also administered to NiV-infected people (Ambat et al. 2019).

Antiviral drugs in progress

Multiple studies have been conducted on developing antivirals against NiV (Fig. 8) (Table 2). According to the Infectious Diseases Society of America, the antiviral drug Ribavirin could be employed to treat NiV encephalitis, even though ribavirin's efficacy in combating NiV is unknown. It causes teratogenicity in animals, and there are several side effects associated with prolonged treatment. Moreover, the therapeutic efficacy of ribavirin, in managing the Malaysian outbreak, as well as the efficiency of acyclovir, used in Singapore, remains unclear (Paton et al. 1999). Due to a lack of effective vaccines and therapeutics against NiV, the National Centre for Disease Control (NCDC) in India has recommended the use of Ribavirin (a guanosine analog) in confirmed NiV cases (Chong et al. 2001). This broad antiviral drug acts on the RNA replication pathway, and was effective against NiV and HeV in in vitro assays. However, when Ribavirin was tested in in vivo animal models, it was found to be ineffective (Georges-Courbot et al. 2006). Ribavirin was found to be effective against acute NiV encephalitis and, as a result, the fatality rate of the NiV-infected patients was reduced by 36% (Chong et al. 2001). The antimalarial drug chloroquine demonstrated its efficacy in cell culture experiments; however, it did not succeed in averting fatalities of NiV-infected hamsters when administered independently or in conjunction with ribavirin (Aditi and Shariff 2019; Ochani et al. 2019).

Remdesivir is another antiviral drug, with wide spectrum potency, that has significantly reduced fatality in

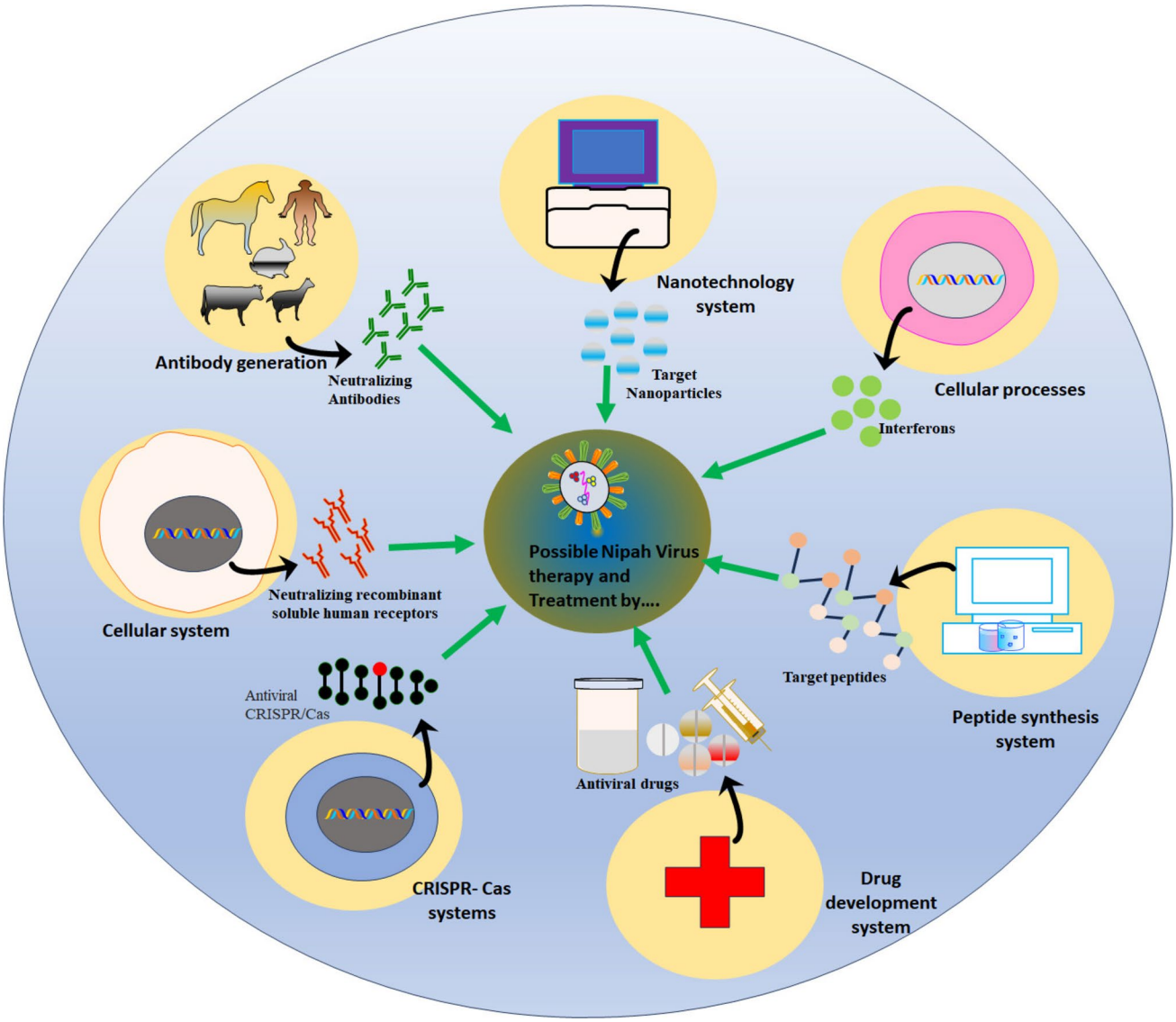

Fig. 8 Different treatment approaches for Nipah virus infection. Representation of the complexity of various possible methods to prevent the virus infection including immunotherapies, nano-therapies, and antiviral drugs

Ebola-infected non-human primates and at the same time showed positive results in in vitro activity against NiV (Lo et al. 2017; Sheahan et al. 2017). Remdesivir is also effective in in vivo animal models and results in 100% survival. Lo et al. carried out a study to test the therapeutic effect of remdesivir against the NiV-B strain in AGMs. The data from that study reported that all the monkeys administrated with lethal doses of the virus survived, and mild respiratory symptoms were observed in a few monkeys (Lo et al. 2019). Amid the COVID- 19 pandemic, remdesivir has been employed in an antiviral treatment regime for SARS-CoV-2 patients, and clinical improvement in infected individuals has been documented, but its efficacy needs to be tested further (Grein et al. 2020; Okoli et al. 2021). A cytidine analog called 4′-azidocytidine or R1479, along with its prodrug balapiravir, is the most recent nucleoside analogs to be tested against NiV (Lo et al. 2017). Balapiravir, a polymerase inhibitor drug, is being looked at as a possible antiviral drug against NiV. In vitro efficacy studies have highlighted the effectiveness of this antiviral agent against both NiV and HeV; however, in vivo, animal studies are further required to validate this. Recently, this drug has also been tested for Dengue virus and hepatitis C virus (HCV), and its narrow therapeutic index and hazardous side effects have been documented (Roberts et al. 2008; Nguyen et al. 2013).

The purine analog T- 705, which goes by the name favipiravir, was subjected to phase II and phase III clinical trials in Europe and the USA, and has received approval for

Table 2 Antiviral drug development against NiV. An overview of antiviral drugs investigated for Nipah virus (NiV) treatment, categorizing them based on whether they are repurposed or newly developed. It also highlights their mechanisms of action, efficacy in in vitro and in vivo studies, and their current stage of development

Strategy	Drug/therapeutic approach	Mechanism of action	Efficacy	Limitations	Repurposed or new?	Stage of development	References
Nucleoside analogues	Ribavirin	Inhibits viral RNA replication	Reduced fatality by 36% in NiV encephalitis cases	Teratogenic; ineffective in in vivo models; side effects	Repurposed (used for other viral infections)	Recommended for emergency use	Chong et al. (2001); Georges-Courbot et al. (2006)
	4′-Azidocytidine (R1479)/Balapiravir	Polymerase inhibition	Effective in vitro against NiV and HeV	Requires further in vivo validation; toxic side effects	Repurposed (developed for HCV)	Preclinical	Lo et al. (2017); Roberts et al. (2008); Nguyen et al. (2013)
RNA polymerase inhibitors	Remdesivir	Inhibits viral RNA-dependent RNA polymerase (RdRp)	100% survival in non-human primates	Needs further clinical testing for NiV	Repurposed (developed for Ebola)	Preclinical for NiV, widely used for SARS-CoV- 2	Lo et al. (2017); Sheahan et al. (2017)
	Favipiravir	RdRp inhibitor	Highly effective in Syrian hamster models	Clinical trials needed for NiV	Repurposed (approved for influenza in Japan)	Preclinical for NiV	Dawes et al. (2018); Lipin et al. (2021)
Antimalarial drug	Chloroquine	Interferes with viral entry and replication	Effective in vitro; ineffective in vivo	Failed to prevent fatalities in hamsters	Repurposed (antimalarial drug)	Preclinical	Aditi and Shariff (2019); Ochani et al. (2019)
Monoclonal antibodies (mAbs)	m102.4	Blocks NiV-G binding to ephrin-B2/B3 receptors	Effective in animal models; approved for emergency use in India	Resistance reported in ferrets and AGMs; side effects	New	Phase I Clinical Trials	Prabakaran et al. (2009); Xu et al. (2013); Playford et al. (2020)
	h5B3.1	Inhibits NiV-F conformational changes	Effective in ferrets	Limited in vivo studies	New	Preclinical	Dang et al. (2019); Mire et al. (2020)
Immunomodulators	Poly (I)-poly (C12U)	Interferon inducer	Prevented NiV-induced deaths in hamsters	More studies needed	-	Preclinical	Georges-Courbot et al. (2006)
Lectin-based antivirals	Griffithsin (GRFT); 3mG	Binds viral glycosylation signatures	Broad-spectrum efficacy (HIV, HCV, SARS-CoV, etc.)	Limited survival rates in hamsters (35% for Q-GRFT; 15% for 3mG)	Repurposed (being evaluated for HIV-1)	Preclinical	Lusvarghi and Bewley (2016); Lo et al. (2020)
Defective interfering particles (DIPs)	DIPs	Reduces viral titers and cytopathic effects	Decreased viral load by 100-fold in vitro	Requires further validation in vivo	-	Preclinical	Welch et al. (2020); Vignuzzi and López (2019)

Table 2 (continued)

Strategy	Drug/therapeutic approach	Mechanism of action	Efficacy	Limitations	Repurposed or new?	Stage of development	References
Vaccine candidates	HeV-sG (subunit vaccine)	Induces cross-immune response against NiV	Effective in multiple animal models; effective against both NiV-M and NiV-B	Ineffective in pigs	New	Phase I clinical trials	Pallister et al. (2013); Middleton et al. (2014)
	mRNA- 1215 (Moderna)	Encodes pre-fusion NiV-F protein	Efficacy yet to be determined	Efficacy undetermined	New	Phase I clinical trials	NCT05398796
	PHV02 (rVSV-based)	Expresses NiV-G and Ebola glycoprotein	Vaccination within 7 days of exposure may protect against severe illness and death	Still in development	New	Preclinical	NCT06221813
	ChAdOx1 NiVB	Adenoviral vector-based vaccine	Efficacious against disease in AGMs	Passive immunity tested only in AGMs	New	Phase I clinical trials	ISRCTN87634044
	rMV-NiV	Recombinant measles virus expressing NiV-G protein	Induced strong immune response in hamsters	More studies required	New	Preclinical	Pedrera et al. (2020)
	Rabies-based vaccine	Live-attenuated vaccine	Evaluated in wildlife	Efficacy under investigation	New	Preclinical	Keshwara et al. (2019)
	Equivac® (Zoetis)	Veterinary vaccine for NiV prevention	Approved for horses; single-dose protection	No human application yet	Repurposed	Approved for veterinary use	Mire et al. (2016); Geisbert et al. (2021)
	Virus-Like Particles (VLPs)	Elicits immune response without live virus	Strong immunogenicity	Requires further validation	New	Preclinical	Walpita et al. (2017)
	Multi-Epitope Vaccine	Designed using immunoinformatics	Non-toxic and non-allergenic	Clinical trials needed	New	Preclinical	Soltan et al. (2021)

treating influenza in Japan. Favipiravir is an inhibitor of viral RdRp and was found to be effective against henipaviruses in Syrian hamster models (Dawes et al. 2018; Sen et al. 2019). According to a recent study, favipiravir appears to have the highest antiviral effectiveness against NiV infection (Lipin et al. 2021). A neutralizing human mAb, called m102.4, was proven to be useful in mice models when administered in combination with favipiravir (Geisbert et al. 2014). Furthermore, among the interferon inducers, poly (I)-poly ($C_{12}U$) showed effective prevention of NiV-induced deaths in hamster models (Georges-Courbot et al. 2006).

Inhibition of viral entry into host cells is an important aspect of antibody-mediated neutralization, both for prophylactic and for therapeutic antiviral therapy. Glycosylation signatures present on the viral surface have also been explored as new targets for antiviral development. Lectins or carbohydrate-binding proteins have been investigated as potent antivirals that specifically recognize glycosylation signatures present solely on the viral surface (O'Keefe et al. 2003; Swanson et al. 2010; Huskens et al. 2010). A mannose oligosaccharide-binding lectin derived from red algae, known as griffithsin (GRFT) protein, has shown broad-spectrum effectiveness against several clinically important enveloped viruses such as HIV, HCV, Herpes simplex virus, SARS-CoV, and SARS-CoV- 2 in both in vitro and in vivo conditions while causing less host damage (Lusvarghi and Bewley 2016). At the same time, the synthetic trimeric tandemer of GRFT called 3 mG is found to be capable of preventing syncytia formation, induced by the G protein of NiV, during infection. Further in vivo studies conducted on NiV-infected Syrian golden hamsters revealed the considerable resistance imparted by oxidation-resistant GRFT (Q-GRFT) and 3 mG against NiV, with 35% and 15% survival rates, respectively (Lo et al. 2020).

Similarly, researchers have explored the use of defective interfering particles (DIPs), as a potential regulator of the dynamics of the viral population that effectively prevents NiV replication. It has been reported that DIPs can effectively decrease viral titers by a factor of 100 and reduce cytopathic effects in Vero cells in in vitro experiments (Welch et al. 2020). DIP genomes are also involved in viral pathogenesis, through various processes, such as viral interference, persistence, and immunological activation (Vignuzzi and López 2019). DIPs can modulate virulence, which has led to an interest in their potential as therapeutic agents. In vivo studies have shown that DIP accumulation reduces disease severity, while the inclusion of DIPs in vaccines increases immunogenicity (Easton et al. 2011).

Immunotherapy

Antibodies can be an effective therapy for NiV infection (Fig. 8). In India, emergency use of mAbs against the F and G proteins of NiV has been permitted (Prabakaran et al. 2009). One of these mAb is m102.4, an affinity matured variety of m102. The development of m102.4 involved phage display panning of a large nonimmune human mAb library against sG_{HeV} (HeV attachment-envelope glycoprotein G), leading to the selection of m102 for its strong neutralization of both HeV and NiV. Affinity maturation using light-chain shuffling and random mutagenesis enhanced m102 binding, resulting in m102.4, which was converted to IgG1 and tested against live viruses. It exhibited exceptionally potent neutralization, with IC_{50} below 0.6 µg/mL and 0.04 µg/mL for HeV and NiV, respectively, binding sG_{NiV} more strongly, despite being selected against sG_{HeV} (Zhu et al. 2008). In 2016, 40 human participants completed a phase I clinical trial in Australia that assessed the immunogenicity, safety, and tolerability of the mAb m102.4 against NiV-G protein. This antibody blocked the attachment of NiV-G to ephrin-B2/B3 receptors located on the host cell surface (Xu et al. 2013). As of now, there were 86 reported side effects related to this course of therapy, with similar frequencies across treated and placebo cohorts; however, no fatalities have been reported in any group so far (Playford et al. 2020). Resistance to m102.4 has also been reported in studies conducted in ferrets and AGMs as post-exposure prevention, following NiV challenge. However, it has been shown in animal studies that m102.4 was effective within 5 days of infection with NiV-M and 3 days of infection with HeV, even after the development of viral viremia and clinical manifestations of the disease (Bossart et al. 2009; Geisbert et al. 2014). Another human mAb called h5B3.1, the humanized version of mAb 5B3, that was developed by immunizing BALB/c mice with NiV glycoproteins, followed by hybridoma generation, through splenic lymphocyte fusion with SP2/0 cells. Hybridomas producing NiV F-specific antibodies were identified via ELISA and immunoprecipitation, then purified using protein G-Sepharose affinity chromatography. mAb 5B3 completely neutralized NiV at 1.5 µg/mL and HeV at 12.5 µg/mL (Chan et al. 2012). It inhibits the conformational changes, required by the F protein of NiV, to initiate membrane fusion, and this mAb has been established to effectively combat NiV and HeV infections in ferrets (Dang et al. 2019; Mire et al. 2020). Despite this, since h5B3.1 is only partially characterized in in vivo experiments, more studies are needed before it can be given to patients, alone or in combination with m102.4.

Vaccine in progress

Based on emerging knowledge, various vaccines against NiV are under investigation. Different vaccine candidates have been or are being explored for the development of vaccines against NiV. Among these different vaccine candidates, few of them have already been proven effective in

in vivo animal experiments. CEPI has been sponsoring the clinical development of more than 30 vaccine candidates against priority pathogens and NiV is one among them. The University of Oxford has started a human clinical trial for testing the NiV vaccine and this trial is supported by CEPI. Several viral vector-based vaccines have been tested such as recombinant proteins from viruses, viral mRNA, and virus-like particles (Broder et al. 2016; Amaya and Broder 2020). Until now, the best candidate has been a subunit-vaccine constructed using the soluble G-glycoprotein of the Hendra virus (HeV-sG; NCT04199169). A human codon-optimized HeVsG construct was cloned into pcDNA-CMV with hygro, transfected into 293 F cells, and developed into a HeVsG-secreting stable cell line. Recombinant HeVsG was produced in serum-free cultures, purified via affinity and gel filtration chromatography, and formulated with Alhydrogel™ and CpG ODN 2007 (Pallister et al. 2011). HeV-sG evokes a cross-protective immune defense against NiV and is under phase I clinical trials. HeV-sG is effective against NiV strains from Malaysia, Bangladesh, and HeV in non-human primates, ferrets, cats, and horses; however, it demonstrates no effectiveness in porcine subjects (Pallister et al. 2013; Middleton et al. 2014). Current research has revealed that HeV-sG can also protect AGMs against the deadly NiV illness 7 days after vaccination (Geisbert et al. 2021).

The mRNA vaccine, mRNA- 1215 (NCT05398796), encodes the secreted stable pre-fusion F protein of the NiV-M strain which is covalently coupled with its G monomer. This mRNA vaccine was collaboratively designed by the Vaccine Research Center (VRC), Moderna, and the National Institute of Allergy and Infectious Disease (NIAID). It was synthesized using T7 RNA polymerase, with N1-methyl-pseudouridine for enhanced stability. It was optimized with Moderna's codon algorithms. After capping and purification, the mRNA was encapsulated in LNPs via ethanol-drop nanoprecipitation and the final vaccine underwent analytical characterization (Loomis et al. 2021; Rodrigue et al. 2024). In 2022, Moderna announced the phase I clinical trials of this vaccine, and the efficacy of this vaccine is still under investigation. The development of a rVSV-NiV chimeric vaccine candidate, called PHV02 (NCT06221813), was also sponsored by CEPI and is currently under pre-clinical trials. PHV02 shares similarities with the Ebola vaccine (Ervebo), as it expresses the envelope glycoprotein of Ebola along with the G gene of NiV. A rVSV-based live-attenuated vaccine system (NCT05178901), encoding F and G protein of NiV, is also under phase I clinical trials. The preclinical studies of this vaccine, in animal models, showed the presence of neutralizing antibodies against the NiV-B strain, within three weeks of immunization, and later protection studies using the NiV-B challenge showed no indications of illness (Mire et al. 2019). Another vaccine candidate, ChAdOx1 NiVB (ISRCTN87634044), was developed by cloning the codon optimized NiV-B G glycoprotein gene into a modified CMV promoter plasmid with TetO sites, and inserting it into a ChAdOx1 genomic clone at the E1 locus. The recombinant ChAdOx1 virus was retrieved, cultured in T-REx- 293 cells, purified via CsCl ultracentrifugation, and titered for vaccination. Phase I clinical trials, conducted by the National Institutes of Health (NIH) and Oxford University, show that this vaccine, which is a viral vector infused with NiV glycoprotein, confers passive immunity in AGMs.

In AGMs, a recombinant measles virus (rMV) expressing NiV G protein, also exhibited similar findings (Pedrera et al. 2020). Recombinant rMV-based vaccines, encoding NiV G, F, and N proteins, were also evaluated in vivo in Syrian hamster animal models. The preliminary data were encouraging, as even the first vaccine dosage elicited a strong humoral immune response (DeBuysscher et al. 2014). To elicit long-lasting humoral immune responses, a live-attenuated rabies vaccine against NiV is being evaluated in wildlife (Keshwara et al. 2019). To date, Equifax®, developed by Zoetis Inc., is the only vaccine legally registered and endorsed by the Australian Pesticides and Veterinary Medicines Authority (APVMA), to treat horses, as a preventative measure. Studies in animals, challenged with NiV, have confirmed that a single administration of this vaccine was found to effectively confer protection. This data provides a rationale for its application in the event of unexpected NiV outbreaks (Mire et al. 2016; Geisbert et al. 2021).

Recently, with the help of immunoinformatics-based approaches, a multi-epitope vaccine was investigated that was based on high-ranking B and T cell epitopes present on selected NiV proteins. The vaccine's physicochemical properties, antigenicity, and solubility as well as allergenicity and toxicity were assessed and were found to be both non-toxic and non-allergenic, although randomized studies are warranted to establish the clinical utility of this vaccine (Soltan et al. 2021). A virus-like particle vaccine (VLP), created from animal cell culture, has also been developed for both native F and G glycoproteins. VLPs create significant immunogenicity and, at the same time, it does not cause any health-related hazards linked with the employment of a virion that contains viral DNA (Walpita et al. 2017). Like mRNA vaccines, pre-fusion F and pre-fusion G proteins elicit strong neutralizing antibody responses (Loomis et al. 2021). Another study found that the pre-fusion F protein has more neutralizing potential than post-fusion F, demonstrating the necessity to maintain the pre-fusion conformation in order to enhance immunogenicity. To encompass a broader spectrum of diversity, in response to various antigenic sites, it is necessary to design a singular vaccine construct having the stabilized antigenic conformations of the prefusion NiV G and F proteins (Loomis et al. 2020). Data have validated that NiV G and F can be potentially effective immunogens for vaccine development; however, to verify the practical

usefulness of this proposed vaccine design, more studies are required. The low number of NiV cases globally creates a hindrance in the development of NiV vaccines, as this results in a low sample size, which becomes inadequate for conducting traditional phase III clinical trials. Additionally, even though the development of NiV vaccines and treatment strategies are urgently needed, it was unlikely to be emphasized during the COVID- 19 pandemic. As a result, a thorough investigation into the progress of NiV vaccines or prospective antiviral therapies is highly suggested.

Perspective

We have witnessed multiple sporadic NiV outbreaks in the last couple of decades. However, comprehensive research into NiV life cycle, transmission, and pathogenesis is still at an early stage. One of the limiting factors in NiV research is that it is a BSL- 4 pathogen, and such facilities are available in limited clinical setups globally, making it a challenging virus to study. Nonetheless, substantial advancements have been made in the fundamental understanding of the virus. The availability of several animal models helps in the extensive research into the nature of NiV, and at the same time makes it easier to test different therapies and design novel vaccine candidates. The high CFR associated with NiV infections, and its limited human-to-human transmission, may reduce the likelihood of NiV causing a pandemic, as it is known that viruses with high fatality rates typically do not spread in wider regions. Due to an error-prone replication machinery of NiV, the possibility of the emergence of a novel strain, with lower mortality and higher infectivity, cannot be ruled out. Hence, it is important to be vigilant, as NiV could evolve into a virulent strain, capable of transmitting itself efficiently across individuals, leading to a global health crisis. To effectively minimize the impact of future outbreaks, we believe that research on NiV should be an important priority of funding agencies, as well as national and international science programs given its high lethality and pandemic potential.

Author contribution RK and SD conceived the project and RM, HAP, RK, and SD wrote the manuscript and designed the figures. NR, SSL and VK, VA, AA, and DK helped with the writing of the manuscript. UY addressed the major revision of the manuscript, and prepared Figs. 1, 2, and 3 and the tables.

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Data availability Data sharing is not suitable for this mini-review paper because no new data was created.

Declarations

Ethics approval Not applicable.

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