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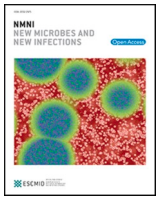

Editorial

One health and bat-borne henipaviruses

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Henipaviruses are a group of viruses that have the capability to be transmitted amongst the bats as well as other animal species and humans through spillover events. The primary viral organisms within this group encompass the Nipah virus (NiV) and Hendra virus (HeV), both of which belong to the genus *Henipavirus* in the family *Paramyxoviridae* [1,2]. The family *Paramyxoviridae* consists of a diverse collection of enveloped RNA viruses with single-stranded negative-sense genome, which infect both animals and humans [3]. The HeV and NiV are the two well-known examples of zoonotic bat-borne viruses that have caused outbreaks with major neurological repercussions in humans. The extensive dispersion of bats over Asia and Africa gives rise to the potential occurrence of seasonal, yearly, and periodic epidemics of these viruses. Bats are becoming recognized as carriers of several zoonotic pathogens, including the henipaviruses [4]. Crowded roosting and high population density of bats densities facilitate the spread of viruses both within and between the species [4]. The primary natural reservoir zoonotic hosts for these viruses have been identified as fruit bats [5]. This editorial explores the clinical implications associated with the zoonotic bat-borne henipaviruses, focusing on the Hendra and Nipah viruses.

Infected people have a 50 to 100% risk of death from these viral infections. Recent research has provided new insights into the mechanisms employed by these to attack viruses to attack the cells, as well as the immune responses that attempt to counteract these attacks. These latest research findings may serve as a template for the development of computer-engineered, next-generation vaccine candidates [6]. Almost annual, outbreaks of NiV have been reported in Bangladesh over the past two decades. The virus has also been detected in the Philippines and India. Humans and *Pteropus* bats in Africa have tested positive for henipavirus antibodies. The current estimation suggests that approximately 2 billion individuals reside in regions where there exists a potential risk of henipavirus spillovers from intermediary animal vectors or bats [7].

1. Epidemiology and transmission

The HeV was first identified in 1994 during an outbreak in the horses and humans in Queensland, Australia. Fruit bats (*Pteropus* spp.), or flying foxes, serve as natural reservoirs of the virus. Although human infections primarily occur through contact with infected horses, resulting in a high case fatality rate (CFR), human-to-human transmission has not yet been confirmed [8]. In horses, the disease typically presents with sudden and severe neurological symptoms, followed by an unexpectedly high fatality rate. Frequent observations have revealed elevated heart rate and respiration rates [9]. According to the available findings, the CFR has been estimated to be 80 % for and 57 % (4/7) in human cases primarily due to fatal encephalitis [10,11].

The NiV is a zoonotic virus that can be transmitted between animals and people. The NiV was initially recognized in 1999 during an outbreak in Malaysia, where pigs were the intermediate hosts. NiV can be transmitted to humans directly from bats or through the consumption of contaminated food, and it has caused several outbreaks with high mortality rates [12]. The majority of infected piglets have been found to lack the clinical disease, while a few exhibit respiratory and neurological symptoms [13]. Low mortality rates (to 1–5%) have been observed across all age groups except infants (about 40 % of the population). Human infections, most likely transmitted through contact with infected pigs' tissues or body fluids, have resulted in severe febrile encephalitis with a CFR of 38 % [14]. The NiV infection is associated with encephalitis and has been linked to mild to severe disease and even death. Nearly every year, outbreaks have been observed in different countries of Asia, most notably Bangladesh and India [12]. Consistent with this, in addition to the known natural hosts i.e. bats, pigs and horses, numerous small animals have been found to be experimentally infectable with henipaviruses promoting viral replication. Current evidence suggests that henipaviruses may be capable of infecting a wide variety of animal hosts [15].

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The recent Nipah virus outbreak in Kerala, India, has raised significant concerns among health care professionals and the general public. The zoonotic illness associated with the Nipah virus has re-emerged in the southern state of Kerala, India. The recent outbreak in Kozhikode, Kerala, led to two deaths out of the six confirmed cases as of September 15, 2023. This is Kerala's fourth Nipah outbreak since 2018 [16,17].

The source of the virus remains unidentified, adding to the challenges of containment. A significant concern is the infection of a 24-year-old health worker, emphasizing the risk to frontline healthcare professionals. Furthermore, 153 health workers have been identified as having come into contact with confirmed cases, potentially amplifying the risk of transmission within healthcare settings. Bats, especially those of the genus *Pteropus*, were identified as potential virus reservoirs. Rapid diagnostics and contact tracing effectively contained the outbreak [18].

2. Consider public health implications

The infection caused by NiV Infection ranges from mild to severe and can result in death due to brain swelling (encephalitis). The manifestation of symptoms normally occurs within a period of 4–14 days subsequent to the individual's exposure to the virus [12]. The disease presents initially as a period of fever and headache lasting between 3 and 14 days, frequently accompanied by symptoms of respiratory illness, such as sore throat, cough, and respiratory distress. Following the initial stage, there may occur a subsequent phase characterized by inflammation of the brain and cerebral edema, commonly referred to as encephalitis [12]. During this phase, individuals may exhibit symptoms such as cognitive disorientation, drowsiness, and mental confusion, which can swiftly escalate to a coma over a period of 24–48 hours. Mortality rates range from 40 % to 75 % in reported cases [12]. According to case reports, six people in the southern Indian state of Kerala have contracted the NiV, which has been transmitted by bats [19]. Out of these cases, two individuals have unfortunately died due to this infection. This outbreak was first identified in late August. Over the past week, over 700 individuals, including healthcare staff members have been tested for infection. This is the fourth Nipah outbreak to strike Kerala in the past five years; the most recent one occurred in 2021 [19]. After an outbreak among Malaysian pig farmers, the NiV was first identified more than two decades ago. A few months later, the transmission of the virus occurred in Singapore via the infected pigs [19]. The outbreak led to approximately 300 reported cases and over 100 deaths. Subsequent to that period, there have been no other instances of NiV outbreaks documented in Malaysia. However, the virus first appeared in 2001 in India and Bangladesh, where it has caused recurring epidemics ever since [20]. On the other hand, the HeV was initially discovered in 1994 in Brisbane, Australia, following the death of a person who had come into contact with infected horses while treating their severe respiratory and neurological condition [20].

Both HeV and NiV exhibit a predilection for neural tissues, a feature that underlies their neurological impact. Fusion between the host plasma membrane and viral membrane is required for paramyxovirus entry into host cells. This process occurs through the interaction of two glycoproteins on the viral surface: an attachment protein (H, G, or HN, based on the extent of neuraminidase and/or hemagglutinin activities) and a fusion protein (F) [21]. These viruses employ ephrin-B2 and ephrin-B3 receptors to enter host cells [1]. This allows them to infect a wide range of tissues, including respiratory epithelium and neural cells. Both F and G are essential for HNV infection, and it has been hypothesized that they endure a series of conformational changes to facilitate virus–host membrane fusion upon receptor engagement [22]. HeV and NiV can enter the central nervous system (CNS) through retrograde axonal transport, resulting in neurological complications [3]. Their ability to invade the CNS is a hallmark of their pathogenesis [23]. The etiology of neuropathogenesis appears to originate from a combination of vascular disease and direct infection of the brain parenchyma. However, the specific contributions of these mechanisms are now unresolved. The infection of the pulmonary epithelial cells and vasculitis are the primary causes to respiratory diseases [24,25]. The neurological implications of these viruses can be severe, as they can cause encephalitis and other neurological symptoms. Infection with the NiV is associated with acute encephalitis syndrome, which can cause seizures, altered mental status, and other neurological symptoms [24]. In humans, HeV infections often present as a febrile illness with respiratory symptoms [23].

The most prevalent neurological complications associated with HeV and NiV infections are encephalitis, seizures, and long-term neurological sequelae including cognitive impairments, motor deficits, and psychiatric symptoms [24–26]. The encephalitis was reported as a prominent neurological complication of both HeV and NiV infections [15]. It arises from the viral invasion of the CNS, causing inflammation of brain tissue. Encephalitis can lead to severe neurological deficits and is associated with a high mortality rate [15]. Symptoms of acute encephalitic syndrome include confusion, sleepiness, ptosis, ataxia, and seizures. Where seizures are frequently observed in patients with HeV and NiV encephalitis [27]. They may result from the inflammatory response within the brain and contribute to further neurological damage [27]. Therefore, understanding the intricate relationship between henipaviruses and their bat reservoirs is essential for disease prevention. Bats seem to tolerate these viruses without developing severe illness, serving as natural hosts and sources of spillover [28].

Henipaviruses are categorized as biosafety level 4 (BSL-4) infections owing to their very high CFR, which have reached up to 70–100 % in current outbreaks. Additionally, the lack of authorized vaccines or treatments for human application further contributes to their classification [29]. Supportive care, including antipyretics and ventilatory support, remains the primary approach. Research into potential antiviral agents and vaccines is ongoing [28,30]. Vaccination of horses against HeV has been implemented in Australia to reduce the risk of transmission to humans. Efforts to develop a human vaccine against NiV are in progress, but challenges remain. In addition to the well-known HeV prototype, specifically, genotype 1 (HeV-g1) and genotype 2 (HeV-g2) (a recently identified variant), was observed in Australian horses exhibiting acute symptoms associated with HeV infection, as well as in flying foxes [31]. The G proteins of both genotypes have a conserved receptor tropism, and the effective neutralization of both HeV-g2 and HeV-g1 was seen when using broadly neutralizing monoclonal antibodies targeting the G and F proteins. Available data indicate that both the post-exposure antibody prophylaxis and equine vaccination targeting HeV-g1 have the potential to be efficacious in combating HeV-g2 [31]. It is worth mentioning that a subunit vaccine, Equivac® HeV, was developed using an oligomeric variant of the HeV G glycoprotein and recombinant soluble, which was introduced in Australia for the purpose of immunizing horses in 2012 [32]. This vaccine represents a significant milestone as the initial authorized veterinary vaccination targeting a biosafety category 4 pathogen. The World Health Organization raised concern about henipaviruses as illnesses with pandemic and epidemic potential that require immediate investigation and development [33]. Controlling outbreaks and preventing zoonotic spillover events requires rigorous public health interventions such as public awareness campaigns, surveillance, and quarantine [23].

3. Intermingling one health concept with the henipavirus zoonosis

Understanding and tackling the complex dynamics of emerging infectious illnesses requires integrating the One Health concept with the research and treatment of zoonoses such as henipavirus infections. Several regions of the globe have been hit by devastating outbreaks of henipaviruses, including the well-known Hendra and Nipah viruses. The complex relationships between wild animals, pets, and people who get zoonotic illnesses underline the need for the holistic approach represented by the one health concept.

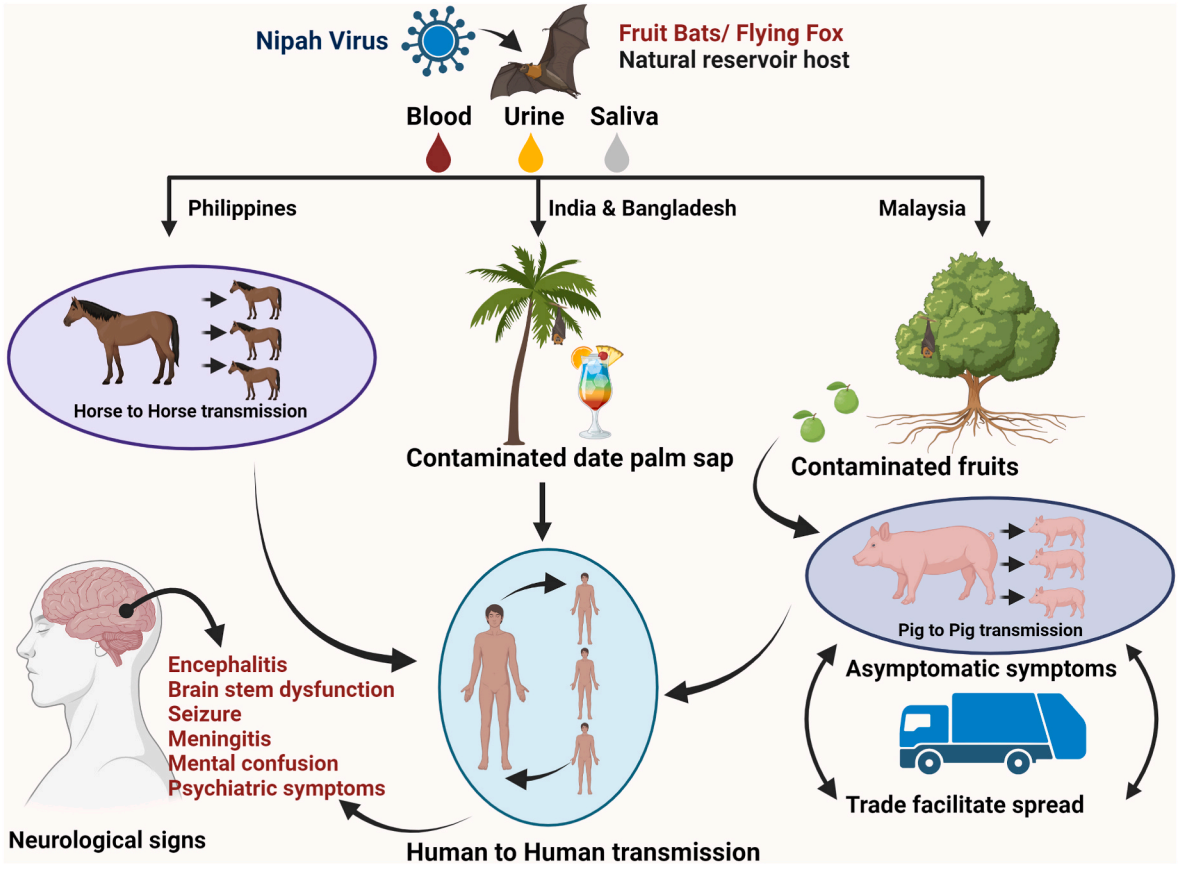

Fig. 1. Schematic representation of transmission routes of different Nipah viruses (NiV). In Malaysia, pig farms lie close to fruit trees, which are resided by fruit bats and domestic pigs contract infection by coming into contact with materials contaminated by bats, particularly by consumption of bat-eaten fruits or exposure to bat urine. NiV is subsequently transmitted from pigs to humans by direct contact. In India and Bangladesh, the primary route of NiV transmission from bats to humans is consuming raw date palm sap contaminated with bat saliva/urine followed by person-to-person transmission occurring by close contact. In the Philippines, the source of human infection was traced to the consumption of horse meat or contact with infected horses, and then human-to-human transmission was reported from infected patients to healthy individuals.

Human, animal, and environmental health are all intertwined, making the multidisciplinary concept of "One Health" so important [34]. It highlights how the origin and spread of henipavirus can frequently be traced back to interactions between these three areas of health and how they are all interconnected. This includes looking into the ecological, veterinary, and societal factors that contribute to the spread of henipavirus zoonosis, in addition to the human health implications of the illness. Useful information regarding henipavirus zoonosis prevention, detection, and impact mitigation may be gleaned from a systemic perspective. The danger of an outbreak of henipavirus can only be accurately assessed by an extensive ecological study that follows bats and their interactions with other species.

The veterinary aspect of one health plays an important part in henipavirus zoonosis, alongside the environmental considerations. Multiple outbreaks have shown that bats may spread the virus to domestic animals like horses and pigs. As a result, keeping an eye on the well-being of pets and livestock is essential for fighting illness. Veterinarians, animal health officials, and government organizations will need to work together on this. Spillover and transmission to humans may be greatly reduced by vaccination of sensitive animals and strict biosecurity measures on farms.

The one health approach emphasizes on working across the various disciplines. Scientists from several disciplines, such as epidemiologists, virologists, ecologists, veterinarians, and social scientists, must collaborate to learn more about henipavirus zoonosis. To provide just a few examples, epidemiologists can monitor human cases, virologists can analyze henipavirus genes, and ecologists can look at bat-wildlife interactions. This pooled information is crucial for developing efficient control and preventive measures. The one health approach to dealing with the henipavirus zoonosis relies heavily on the efforts of public health and medical personnel. Infected people are diagnosed and treated, monitoring systems are set up, and public health initiatives are created under their purview. Due to the possibility of henipavirus transmission between humans, prompt and precise diagnosis is of the utmost importance. Infected people may be kept from infecting others by proper case management and isolation. In addition, medical personnel need to be made aware of the dangers posed by these infections and provided with appropriate safety gear.

The social sciences are also very important in the one health paradigm. In order to reduce the likelihood of zoonotic disease transmission, it is crucial to have a deeper understanding of human behaviour and communities' relationships with wildlife and domestic animals [35]. Researchers in the social sciences may look at the cultural practices, land use patterns, and economic variables that contribute to human encroachment on natural environments. Public health campaigns, education programs, and policy decisions may be better informed by this information, lowering the chances of zoonotic spillover of the henipavirus.

The effects of deforestation and urbanization on henipavirus zoonosis are examples of the environmental changes that fall within the purview of the one health concept. These landscape changes have the potential to disturb ecosystems, raising the likelihood of secondary effects. Sustainable land-use practices and regulations that take into account the effects on wildlife and human health are promoted by

proponents of the "One Health" approach. The danger of zoonotic transmission may be lowered by keeping bat and other animal habitats unaltered and by reducing human-wildlife conflict [36]. Research and treatment of zoonotic diseases like henipavirus need a worldwide perspective, which is what the one health approach provides. There have been outbreaks of these viruses in numerous nations, and the transmission of the illness may be facilitated by the movement of people, animals, and things across the borders. When it comes to exchanging knowledge, skills, and resources, international collaboration is important. Early warning systems for probable outbreaks may be provided by collaborative research and monitoring networks, allowing for prompt actions to be taken and the illness contained.

Climate change is one of the several variables that have been connected to the spread of henipaviruses. Bats and the host species they interact with may be affected by shifts in temperature and precipitation patterns. In order to foretell the geographical range of henipaviruses and identify the places at increased risk of outbreaks, an understanding of these climate variables is crucial. Through a well-coordinated collaborating, the climate scientists, ecologists, and epidemiologists can create models that predict how the virus will spread in the future. Risk communication and community involvement are also key to the one health philosophy [37]. Educating communities, medical professionals, and politicians about the dangers of henipavirus zoonosis is crucial. People are more likely to take preventative actions like avoiding contact with animals and maintaining excellent hygiene if they are informed in a clear and convincing manner. It may also assist the communities and authorities to work together facilitating the implementation of control initiatives.

Overall, a more thorough and successful approach to contain this emerging infectious illness requires incorporation of the one health concept with the investigation and treatment of henipavirus zoonosis. The factors driving the emergence of henipaviruses can be better understood, and more effective strategies can be outlined to prevent and control their spread, if we recognize the interconnections between human, animal, and environmental health and foster collaboration among the various disciplines. Aligning with the larger aims of supporting a healthy world, this holistic approach has several positive effects, including improvements in the public health dimension, biodiversity preservation, and ecological sustainability [38–42].

In conclusion, the zoonotic bat-borne henipaviruses specifically the Hendra and Nipah viruses, pose significant clinical implications for animals and humans. Understanding their epidemiology, pathogenesis, clinical manifestations, and management is vital for preventing and controlling the outbreaks. Addressing the complex interplay of virus-host interactions, ecological factors, and health consequences requires a multidisciplinary approach and continued research efforts in the hidden corners where these viruses reside. .

Data availability statement

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

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Ethical approval

This article does not require any human/animal subjects to acquire such approval.

Author contributions

Om Prakash Choudhary: Conceptualization; Software; Investigation; Data curation; Writing – Original Draft; Writing – Review & Editing; Supervision; Project administration. **Priyanka**: Conceptualization; Data curation; Writing – Original Draft; Writing – Review & Editing. **Mai Abdel Haleem Abu Salah**: Conceptualization; Data curation; Writing – Original Draft; Writing – Review & Editing. **Hitesh Chopra**: Data curation; Writing – Original Draft; Writing – Review & Editing.

Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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