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Pandemic potential of henipaviruses

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ABSTRACT

Introduction and purpose. Hendra and Nipah are two highly dangerous zoonotic viruses belonging to the group of henipaviruses. Although they have been known for over 20 years, no human drug or vaccine has been invented. This paper aims to to describe the epidemiology of the reported paramyxoviruses, the pandemic potential of henipaviruses, and a standardised action plan to counter their spread. This paper reviews scientific articles from 2012-2023 published in scientific databases such as Pubmed, Researchgate, and Google Scholar. The keywords used were pandemic potential of henipaviruses, Hendra virus, Nipah virus, and henipavirus epidemics.

State of knowledge description. The mortality rate of henipaviruses varies between 50 and 100%. The Nipah virus is particularly dangerous, with epidemics recurring virtually every year in Asia since 1998. The Hendra virus situation may be manageable because there is an effective vaccine for horses most vulnerable to infection. Due to human activity, the habitats and climate of the animals serving as virus reservoirs are changing. Because of frequent henipavirus outbreaks in Asia and Australia, extensive efforts are being made to contain and neutralise them rapidly.

Conclusions. As henipaviruses pose a high pandemic threat, more research into drugs and vaccines is required. It is also essential to develop effective bio-assurance plans, introduce controls on their operation and educate the population on the issue. Reservoir animals, through anthropogenic environmental changes, are changing habitats and feeding sites, making more and more territories vulnerable to the disease. New species of henipaviruses constantly emerge and pose an epizootic challenge to public health. Hence, an essential action is to increase the amount of research into the virus's epidemic development and conduct it as widely as possible.

Introduction

Paramyxoviruses are a group of single-stranded RNA viruses with negative polarity. They belong to the family Paramyxoviridae and the order Mononegavirales [1,2]. The Henipavirus genus viruses, Hendra (HeV) and Nipah (NiV) are a severe public health concern. They cause local epidem-

ics of Hendra and Nipah viral diseases with high mortality rates. Therefore, unique bio-assurance plans are being implemented in vulnerable areas to protect against the potential development and spread of the disease. The lack of defined treatment and vaccines qualifies them as biosafety level 4 pathogens. NiV has been recognized by the WHO as a global health problem and listed as an epidemic threat and biological weapon [3,50]. Henipaviruses can be a high-risk threat due to their lack of a human vaccine, zoonotic disposition and confirmed cases of human-to-human transmission [4].

Fruit bats, particularly Pteropus, are natural reservoirs of pathogens. In Australia, all four species of flying foxes that were studied (Pteropus alecto, Pteropus poliocephalus, Pteropus conspicillatus, and Pteropus Scapulatus) were found to carry the virus, with a particular emphasis on Pteropus alecto and Pteropus conspicillatus. The virus asymptomatically circulates between individuals of bats thereby maintaining continuity of existence and replication [5]. There are two mechanisms of infection, one exemplified by the outbreak in Malaysia – transmission of the virus through animals, from bats to horses to pigs to human infection or transmission of the virus straight from bat to human observed in Bangladesh and India. In the Philippines, transmission has been seen through the consuming contaminated, unwashed, raw date palm fruit [6,7].

Disease and symptoms of henipavirus infection

Nipah virus disease is a zoonosis. Frugivorous bats transmit the pathogens causing it. The possibility of transmitting the virus through close contact with infected body fluids of infected animals has been documented, and very rarely among humans. However, the transmission of the infection via droplets is doubtful. It has been experimentally found that the amount of virus in saliva, throat secretions, and urine is small. It was first recorded in Kampung Sungai Nipah in Malaysia in 1998 among pigs. It manifested mildly in animals with respiratory and nervous system syndromes. At the same time, in humans, high fever was observed, and ARDS were observed in approximately 50–60%; a few days after infection, mental status changes, visual paralysis, areflexia and limb weakness appeared. Patients' condition often deteriorates rapidly, with symptoms suggestive of brain stem involvement, leading to coma and death within a few days. In the cerebrospinal fluid, lymphocytic pleocytosis and raised proteins with normal glucose levels are observed. [16,47]. Nipah disease observed among the Malaysian and Singaporean populations began with a sudden increase in body temperature, headaches and dizziness, vomiting and thinner stools – mild, unusual symptoms of a viral infection. Nervous system symptoms such

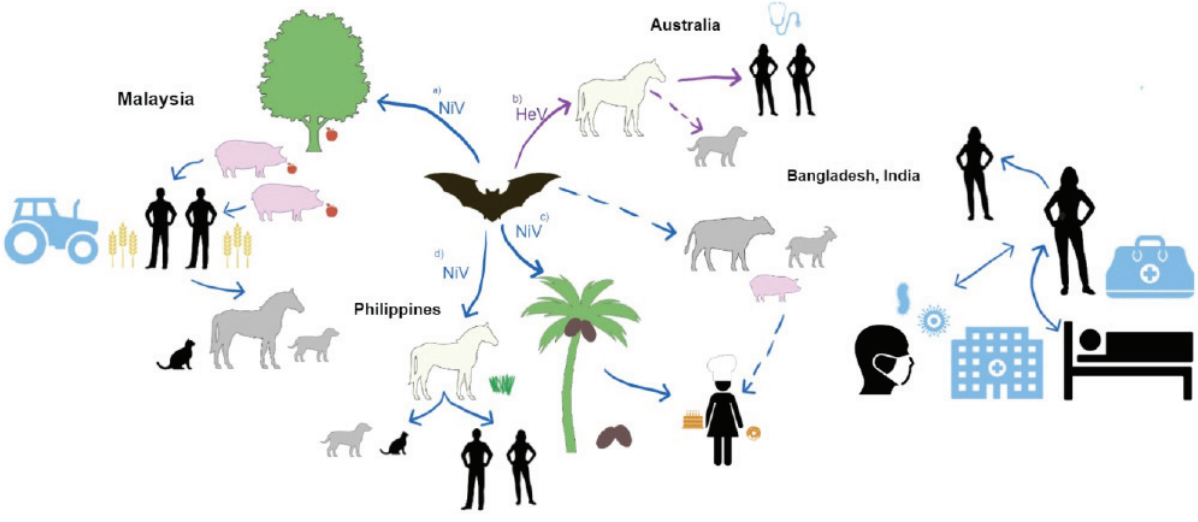

Figure 1. Virus transmission pattern by country based on available studies [8,9,11,12,20,22,24,25].

as loss of consciousness, areflexia, and a drop in blood pressure followed, and some patients also suffered from epileptic seizures. The most severe post-infection symptoms are encephalopathy and atrophy of the white matter of the brain. Behavioural changes and motor paralysis of some muscles are also observed [17–19]. The infection has been reported to be asymptomatic in 8% of infected people. [20]. The clinical manifestations described vary depending on disease location. The epidemic in Malaysia had a lower mortality rate than epidemics in India or Bangladesh [21]. In the Malaysian Nipah disease epidemic, nervous system syndromes played a key role. In contrast, during the epidemics in India and Bangladesh, respiratory failure, acute cough and atypical pneumonia symptoms were observed among patients [22,23]. Nipah virus infection, regardless of region, most often leads to severe encephalitis and death [24]. Nipah should be differentiated between Japanese encephalitis, malaria of the nervous system and rabies. Magnetic resonance imaging and laboratory tests are helpful in differential diagnosis [3,27].

Epidemic in Malaysia and Singapore

In September 1998, the first infections of unknown aetiology were observed among pigs and farmers near the town of Ipok. Subsequent cases were registered in the towns of Sikamat and Bukit Pelandok. At first, the illness was believed to be caused by the Japanese encephalitis virus. However, it was soon discovered that a different pathogen, the Nipah virus, was the actual cause of the disease, as mainly adults and people who had been vaccinated for Japanese encephalitis were still contracting the illness [24,25]. Nipah virus is primarily transmitted through contact with the bodily fluids of infected pigs, such as faeces, urine, and saliva. Adult males associated with swine farms were most at risk of contracting the disease. Interestingly, native Malays, as followers of Islam, are not allowed to have close contact with pigs and also are not allowed to consume pork, so among their population, no case of infection has been reported [8]. The disease has spread to Singapore through numerous negligence in controlling exported goods, and most likely through uncontrolled pork and pig livestock shipments. Initially, illnesses were reported among slaughterhouse workers, but then the disease developed in pig farmers who also participated in pig transits from infected Malaysia [25]. In order to eradicate the epidemic, the transportation of pigs was banned, preventive culling of exposed or sick animals was used, and educational activities and national sanitary surveillance were carried out. In Malaysia, the primary industry is pork production. The preventive culling of more than a million animals caused substantial financial losses. However, the measures taken in both countries brought good results, and the epidemic was halted. The last disease was found in May 1999; no case has been found since then [4,19].

Epidemic in India and Bangladesh

In early 2001, numerous cases manifesting as acute fever combined with impaired cognition and concentration were observed near the city of Siliguri in India. Pathogen isolates that had been previously tested were compared to samples collected during a viral outbreak in Bangladesh. It was noted that there was a similarity between the two as both samples showed the presence of NiV henipavirus. Additionally, another outbreak was identified in West Bengal, where five cases were reported, and each turned out to be fatal. The largest outbreak of the Nipah virus in India was reported in Kerala in 2018; 23 patients were reported, of whom 18 died; thus, the disease mortality rate was 91% [25–27].

In contrast to Malaysia and Singapore, in Bangladesh and India, the leading infectious agent of NiV was the consumption of date palm juice or contact with a sick person. In India, the contagion's spread mechanism relied mainly on the zoonotic potential of the virus, bat-to-human, human-to-human transmission. The danger of this case was also posed by domestic animals, which could transmit the virus. The last Nipah virus infection was reported in the second week of September 2023 in the southern Indian state of Kerala. Six cases were reported, including two deaths. Kerala faced the presence of the virus for the fourth time. The region's authorities took immediate action to prevent the spread of

the virus. Schools, offices and public transport in Kozhikode district were closed, and wearing masks in public places was imposed. No further cases of the disease have been reported since September 15. [44,45] The epidemic in Bangladesh began in Mehepur district in 2001, with 13 cases reported. Since then, numerous outbreaks have been observed yearly in different parts of the country until 2015, and the virus' mortality rate has remained at 76.2%. During the outbreak in Bangladesh, 261 cases, including 199 deaths, were reported. Cases of person-to-person transmission have also been reported among the Bangladeshi community, although the risk of such transmission is very low [11,22,24,27,49].

Epidemic in Australia

In late 1994, in the Brisbane area of Hendra, previously unknown respiratory symptoms with hemorrhagic symptoms were observed among horses in a suburban stable [10]. Twenty horses became ill, of which 13 died and their trainer, who successively lost his life as a result of respiratory and kidney failure. The next epidemic case was reported in another part of Australia – Queensland – it involved two horses and one human who died of recurrent encephalitis [8,9]. The virus has been identified in 50 outbreaks. By 2021, 105 horses had died of HeV in Australia. Several bio-assurance measures have been taken to control the outbreaks; these have mainly consisted of increasing the hygiene of watering holes, regular cleaning, changing the water as frugivorous bat secretions could be found there, regular decontamination of stables, testing horses for HeV and preventive culling in case of illness [12]. Hendra virus infection may carry the stigma of an occupational infection because, in Australia, the most common source of infection was the transmission of the virus from horses to humans, which mainly exposed horse breeders and veterinarians. [18,31,41]

Virus detection

According to WHO, the preferred diagnostic method is qRT-PCR due to its high sensitivity and specificity. Immunochemical tests, ELISA antibody detection tests, and virus neutralization tests, which can be performed in high-class BSL 3+ and BSL L4 safety laboratories, are also used. These tests are the reference standard in serological diagnosis of NiV and HeV. To increase the scale of testing and enable lower-class laboratories to perform them by being able to work on irradiated viral antigens that are thus neutralized and come from cell cultures [24,28,46–48].

Treatment and prevention methods

Testing serum IgM levels has detected the virus, and diagnostic methods such as polymerase chain reaction-PCR and real-time PCR performed on tissue material or cerebrospinal fluid have also been used [24,28].

Treatment of Hendra virus is problematic due to the need for more effective drugs. Studies have been conducted on hamsters using ribavirin and chloroquine and their combinations but have yet to show positive results [21]. Currently, research is being conducted on recombinant monoclonal antibodies, but the efficacy of this therapy is low [9,12]. In 2012, Zoetis Australia launched Equivac® HeV vaccine for horses. This vaccine is administered in two doses three weeks apart. Three weeks after the second dose, antibodies that effectively protect against the disease are formed. A booster dose is given after six months, with subsequent booster doses every 12 months. Equivac® HeV has side effects but are mainly local and occur in 0.001% of horses tested [10,29]. Breeders are often reluctant to vaccinate horses because they believe the vaccine negatively affects horses' athletic performance, a myth debunked by a large study [30]. The vaccine is effective for non-human monkeys, although more research is needed to test its effectiveness in humans [12].

Currently, there is no targeted treatment for Nipah virus infection. Ribavirin is used as an adjuvant treatment. During the 1998–1999 outbreak in Malaysia, it was administered to some infected patients, and it was found that among them, the mortality rate was 36% lower than the control group [2]. During the 2018 outbreak in Kerati, India, ribavirin gave patient treatment results, but the study group was too small to draw firm conclusions [23]. Studies in animal models do not support the efficacy of ribavirin [7].

There have been many attempts to invent a drug targeting the Nipah virus, and the most promising studies involve monoclonal antibodies against the G protein of Henipavirus (m102.4) [13,23]. The m102.4 monoclonal antibody neutralizes HeV, NiV-M and NiV-B viruses. In animal model studies, administration of the antibody after exposure to the virus protected against disease. The antibody was administered to 14 people, and no side effects were registered. There are other hope-rising ongoing studies on other antibody h5B3.1 [31].

Currently, there is no registered vaccine against the Nipah virus. Much research is underway on different types of vaccines, many of which are effective for animal models [31–34]. Recently, an HeV vaccine against the Hendrach virus was found to protect African Green Monkeys from the Nipah virus [24,35].

Discussion

The world has been facing Henipavirus epidemics for about 30 years. After the COVID-19 pandemic, more attention is being paid to the threat posed by the viruses, and the scientific world is more focused on developing new strategies to combat epidemics [36]. They are particularly dangerous because their mortality rate oscillates between 50–100%, and no specific treatment has yet been developed. Particular attention should be paid to the Nipah virus, which has caused epidemics for over 20 years, almost yearly [5]. It has a high pandemic potential, as no drug or vaccine has been developed for it; the bats that spread it are found in almost all of Asia, and pigs, which are raised practically all over the globe, may also be involved in spreading the virus [1,31,33,36]. When considering the pandemic nature of the Nipah virus, it is worth focusing on bats since they migrate seasonally over long distances, contributing to the spread of the disease [26]. Through deforestation of the land, bat roosting and foraging sites are changing. It has been postulated that climate warming may change their roosting areas, contributing to outbreaks in places where they did not previously occur [22,37,38]. Only for the Hendra virus is there an effective horse vaccine that effectively stops outbreaks from developing [8,9].

Nipah and Hendra are the two main species of henipaviruses, but not the only ones. Mutations always lead to the emergence of new types [2,39]. In 2021, a new henipavirus, Langay, appeared in China; its reservoir is shrews, from which humans are infected. There is no evidence that the disease can be transmitted from human to human, but it is not excluded [15,40]. Its symptoms are usually not dangerous, but fatal cases have occurred. Somewhat reminiscent of the symptoms of COVID-19, LayV manifests mainly with fever, fatigue, muscle aches and respiratory symptoms – mainly cough and shortness of breath [39,41].

Due to the lack of effective treatment, available vaccines and high mortality rates, henipaviruses are a significant public health challenge. The current state of knowledge on treatment and epidemiology is inadequate; so more research is essential [3,6,31,42].

Conclusions

1. Henipaviruses have a high pandemic potential, so research needs to focus on the epidemiology of individual species.
2. Climate change and deforestation are likely to change bat migration routes and areas, so changes in bat habitat should be studied.
3. More research is needed on numerous research and control groups on the treatment of henipaviruses.
4. Because of how deadly some henipaviruses are, it is crucial to develop a vaccine as soon as possible.
5. Due to the lack of targeted treatment for henipaviruses, it is imperative to raise awareness about them within the countries where they occur.

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