



An impending public health threat: analysis of the recent Nipah virus outbreak and future recommendations – an editorial

Amogh Verma, MBBS^a, Hritvik Jain, MBBS^b, Samia A. Sulaiman, MD^e, Prakriti Pokhrel, MBBS^{d,*}, Aman Goyal, MBBS^c, Tirth Dave, MD^f

Dear Editor,

A recent outbreak of the novel Nipah virus (NiV) in Kerala, India, led to the death of the first patient on 30 August 2023, followed by the second patient on 11 September 2023. Virological evidence has demonstrated that it is the same virus strain which led to the Bangladesh outbreak. In early 2023, a total of 11 cases, including eight deaths, were reported, which is significantly higher than the typically lower annual number of reported cases^[1,2]. In addition to the two deaths, six other patients tested positive for NiV. Currently, the source of the virus is being investigated, 43 containment zones were created by the health authorities, and samples from half-eaten fruits and the urine of bats are being tested for the NiV in Maruthonkara village, Kerala, where the first patient lived^[3].

NiV is a zoonotic virus, meaning that it spreads between animals and humans. NiV belongs to the *Paramyxoviridae* family, which comprises single-stranded RNA viruses and belongs to the *Henipavirus* genus. In addition, NiV has been internationally classified as a Biosafety Level-4 pathogen^[4].

The incubation period for the NiV is estimated to range from 4 to 14 days but could also last up to 45 days^[4]. Currently, no research demonstrates the viral persistence of NiV in bodily fluids or in foods^[4]. Fruit bats could spread the disease to humans and to animals, including pigs, which could subsequently be spread to other individuals in close contact with animals or their bodily fluids (Fig. 1). Once a person is infected, the spread of NiV can

also happen via person-to-person contact or their body fluids, including respiratory droplets, urine, or blood^[5]. Nosocomial infection has also been observed, where reports have demonstrated that 75% of NiV cases in Siliguri, India, took place in a healthcare setting in 2001. Therefore, the NiV could be transmitted to humans through various established routes^[4,5]. The consumption of food products contaminated by the body fluids of infected animals, such as palm sap or fruit contaminated by an infected bat, is also another mode of transmission^[4,5].

The current NiV outbreak is the fourth outbreak that the state of Kerala has witnessed, the most dangerous of which took place in 2018, forcing the authorities to announce 8 containment zones, with 21 reported deaths among the 23 infected patients. The 2019 and 2021 outbreaks each reported one death and were better controlled, the latter involving a 12-year-old boy dying from the virus, with heart inflammation and brain swelling^[3,6]. In addition to the ongoing investigation regarding the source of the virus, mass testing has been commenced to control and evaluate the spread of this disease, where 950 contacts have been identified, including 213 healthcare workers. Approximately 76 individuals in close contact with confirmed cases are being monitored for developing symptoms, while 700 others including 153 healthcare workers, are presently being tested for the virus^[3,6]. All medical staff in contact with the confirmed cases are being isolated following strict hygiene measures. These measures include the use of personal protective equipment (PPE) to avoid direct contact with patients' secretions and excretion^[4,7]. Individuals attending funerals of the deceased infected patients have also been isolated, with four more active cases. Moreover, all educational institutions have switched to online teaching until the 24th of September. Health authorities advise citizens to be vigilant regarding the common symptoms of NiV infection. The neighbouring state of Kerala, Tamil Nadu, announced that any travellers coming from Kerala are to be tested and that any with flu-like symptoms will be isolated^[6].

Previous outbreaks of NiV occurred in Bangladesh, India, Malaysia, the Philippines, and Singapore. The first known outbreak took place in 1998–1999 in Malaysia, infecting 300 individuals and killing over 100 individuals. It had also spread to Singapore, where 11 patients and one death were recorded after being exposed to imported pigs from Malaysia. Since then, the World Health Organization (WHO) has reported over 600 cases between 1998 and 2015. In 2018, Kerala, India, experienced its deadliest outbreak, with 21 reported deaths among the 23 infected patients. Subsequent outbreaks in 2019 and 2021, also in Kerala, India, were comparatively better controlled, each resulting in one reported death. Early in 2023, a concerning situation

^aRama Medical College Hospital and Research Centre, Hapur, ^bAll India Institute of Medical Sciences (AllMS), Jodhpur, ^cDepartment of Internal Medicine, Seth Gordhandas Sunderdas (GS) Medical College and King Edward Memorial (KEM) Hospital, Mumbai, India, ^dKathmandu Medical College and Teaching Hospital, Kathmandu, Nepal, ^eSchool of Medicine, University of Jordan, Amman, Jordan and ^fBukovinian State Medical University, Chernivtsi, Ukraine

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*Corresponding author. Address: Kathmandu Medical College and Teaching Hospital, Kathmandu 44600, Nepal. Tel.: +977 9845369499. E-mail: prakriti.pokhrel@kmc.edu.np (P. Pokhrel).

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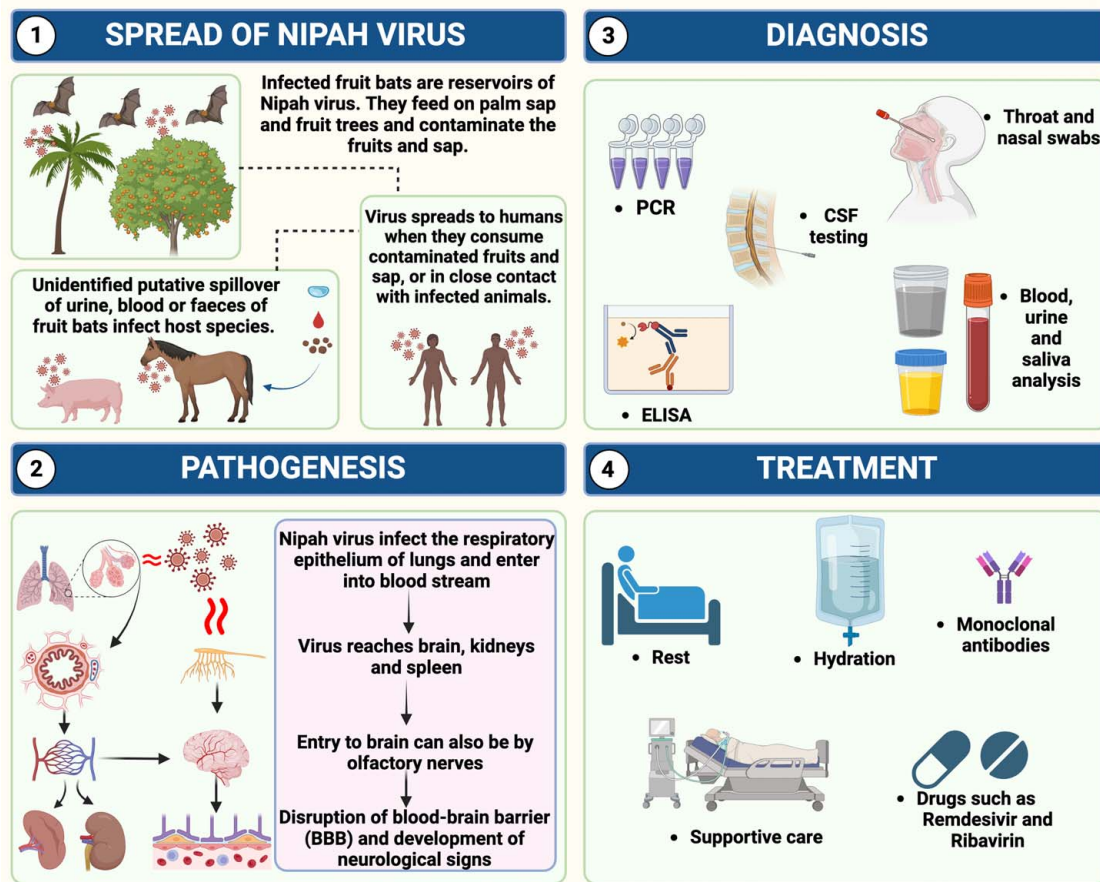


Figure 1. Spread, pathogenesis and clinical management of Nipah virus infection – (1) Spread of Nipah virus: The virus could spread between animals and people through close contact or by bodily fluids. (2) Pathogenesis: Nipah virus infects the epithelium of the lungs and enters the bloodstream, through which it travels to the brain, kidneys and spleen, impacting the olfactory nerves due to entry into the brain. Finally, neurological signs begin to develop after the blood–brain barrier (BBB) is disrupted. (3) Diagnosis: Polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), cerebrospinal fluid (CSF) testing, throat and nasal swabs, and blood, and urine, and saliva analysis are the tests to confirm a positive case of Nipah virus infection. (4) Treatment: Antiviral medications including remdesivir and ribavirin, and monoclonal antibodies are used to combat the virus, alongside hydration, rest, and supportive care.

emerged in Bangladesh, with a total of 11 cases and eight deaths reported. In August and September of the same year, Kerala, India, witnessed another outbreak. Tragically, the first patient succumbed to the virus on 30 August, followed by the second patient on 11 September. Additionally, six more patients tested positive for the Nipah virus during this period, marking a resurgence of this concerning disease in the region^[8–12].

According to the Centers for Disease Control and Prevention (CDC) and WHO, the overall global case fatality rate (CFR) for the NiV is 40–75% between 1998 and 2018 and is dependent on the availability of prompt and quick management of cases as well as epidemiological surveillance^[2,5].

The first identification of NiV dates back to 1998–1999 in the Sungai Nipah village of the Malaysian peninsula, from where the name ‘Nipah’ originates^[5]. Then, NiV manifested itself as an outbreak of encephalitis and respiratory illness among pig farmers and other individuals who were in close contact with pigs^[5]. In 1998–1999, NiV affected Malaysia and Singapore, then it went dormant for 2 years but later caused another outbreak in geographically non-contiguous countries like Bangladesh and India in 2001, where genetic sequencing revealed a different strain of NiV than the one sequenced in 1999^[5]. Since

then, NiV outbreaks have been nearly annual in Bangladesh since 2001 and periodic in India^[4]. No other outbreak has been reported in Malaysia and Singapore since 1999^[4]. The major difference between the 1998–1999 outbreak and the 2001 outbreak was reported to be human-to-human transmission in 2001, which was not described in the 1998–1999 outbreak^[13]. The Siliguri outbreak in India was attributed to a single patient admitted to a hospital who infected 31 individuals^[14]. In 2014, another NiV outbreak was observed in the Philippines, which was attributed to infected horses^[15]. In 2018, the district of Kozhikode, India, suffered a NiV outbreak with CFR as high as 89%^[15]. The most rampant NiV outbreak was the 1998–1999 Malaysian outbreak, which claimed more than 100 deaths^[5].

The major risk factor for NiV spread is the abundance of its natural reservoir, fruit bats belonging to the genus *Pteropus*^[5]. The presence of fruit bats in several tropical countries like Cambodia, Indonesia, Madagascar, the Philippines, and Thailand has been identified as a risk factor for potential NiV outbreaks in the future too^[4]. Consumption of raw date palm sap contaminated by infected fruit bats has been demonstrated to transmit NiV^[16]. Fruit bats can shed the virus cyclically, with numerous factors affecting the pattern of shed including

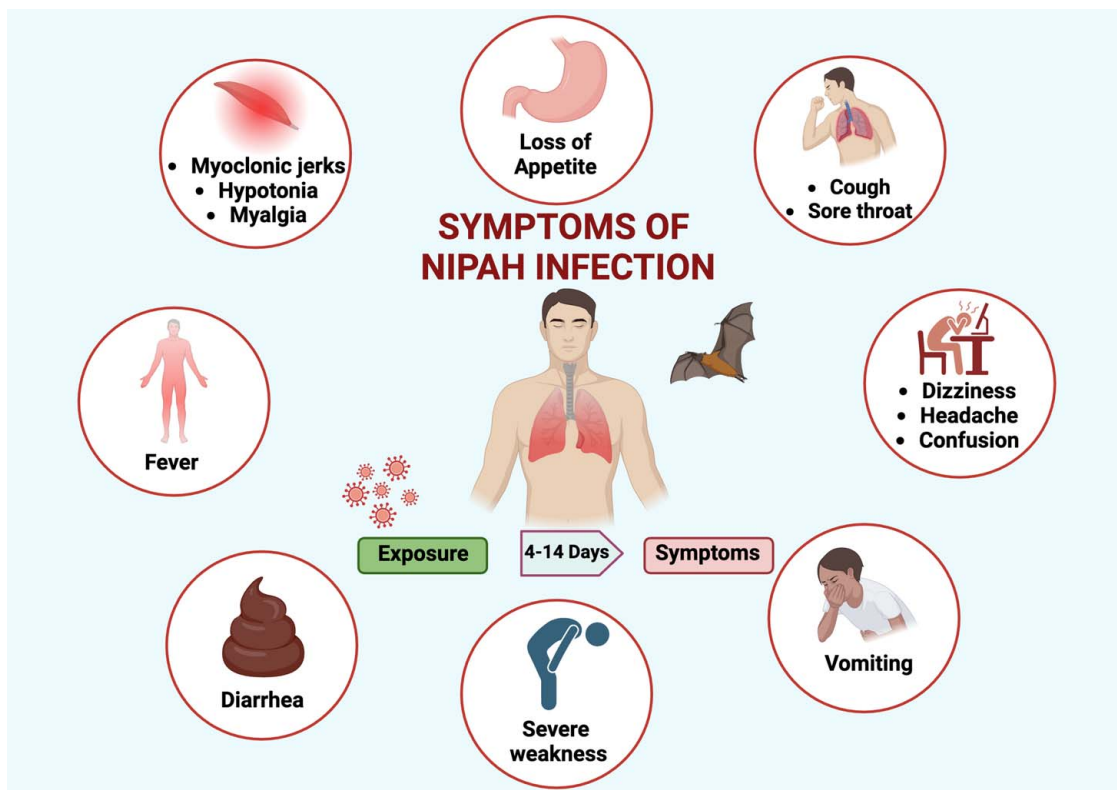


Figure 2. Symptoms of Nipah infection – After exposure to the Nipah virus, a latency period of 4–14 days ensues, during which symptoms begin to manifest as flu-like disease in the early stages and later progress in their severity. These symptoms can be categorized into four groups: Respiratory symptoms encompassing cough and sore throat, central nervous system (CNS) manifestations including dizziness, headache and confusion, and gastrointestinal symptoms including loss of appetite, vomiting, severe weakness, diarrhoea, and fever. Lastly, muscle disorders are represented by myoclonic jerks, hypotonia, and myalgia.

population turnover of bats, migration of infected bats, and some immunological factors^[17].

NiV infection in humans is characterized by a variable incubation period, spanning from 4 days to up to 2 months, with over 90% of infected individuals typically exhibiting symptoms within 2 weeks of exposure. Initial symptoms can include fever, headache, cough, sore throat, breathing difficulties, and vomiting, progressing to severe symptoms such as disorientation, drowsiness, confusion, seizures, and even coma, often associated with encephalitis and brain swelling (Fig. 2). Neurological complications, including sensory abnormalities, abnormal pupillary reflexes, vasomotor changes, and myoclonus are common, with some cases manifesting as meningitis, diffuse encephalitis, or focal medulla oblongata involvement. Concurrently, atypical pneumonia and severe respiratory issues, including acute respiratory distress may develop. Survivors of acute encephalitis can experience long-term sequelae, including relapses or delayed encephalitis, sometimes occurring months or years after the initial infection, often accompanied by psychiatric symptoms such as depression, personality alterations, attention deficits, and memory deficits^[4,5]. The mortality rate of NiV infection varies, ranging from 40% to 75%. However, up to 11% of individuals remain asymptomatic, and this proportion depends on the specific infecting NiV strain. In severe cases, encephalitis and seizures can rapidly progress, often leading to coma within 24–48 h, signifying a poor prognosis, with death typically occurring within a median of 6 days after symptom onset^[18].

Early diagnosis is pivotal in effectively managing and containing NiV outbreaks while ensuring appropriate patient care. Various diagnostic approaches are available, spanning serological, molecular, virological, and immunohistochemical methods. Serological techniques employ enzyme-linked immunosorbent assays to detect NiV antigens and antibodies, complemented by virus-neutralization tests to ascertain the presence of specific antibodies. Molecular biology methods, particularly PCR (polymerase chain reaction), stand as the gold standard due to their high sensitivity and specificity for NiV detection. Viral isolation entails culturing samples in Vero cells, followed by immunostaining, seroneutralization, and PCR for virus identification. Immunohistochemistry employs anti-NiV antibodies to stain formalin-fixed tissues, facilitating the identification of viral antigens. Timely specimen collection in the early disease stages is critical, typically involving throat and nasal swabs, cerebrospinal fluid, urine, and blood samples^[19,20]. Human-to-human transmission is also a documented risk, emphasizing the importance of avoiding contact with infected individuals in these regions^[5].

NiV is transmitted through direct contact with animals or their bodily fluids, contamination of food with the body fluids of infected animals, and even person-to-person transmission, especially in countries such as India^[5]. The most common animal notorious for spreading the virus is the fruit bat^[5]. Recurrent NiV outbreaks in Kerala might be due to the large population of bats in the state, which frequently harbours this virus. The public health authorities of Kerala decided to shut down educational

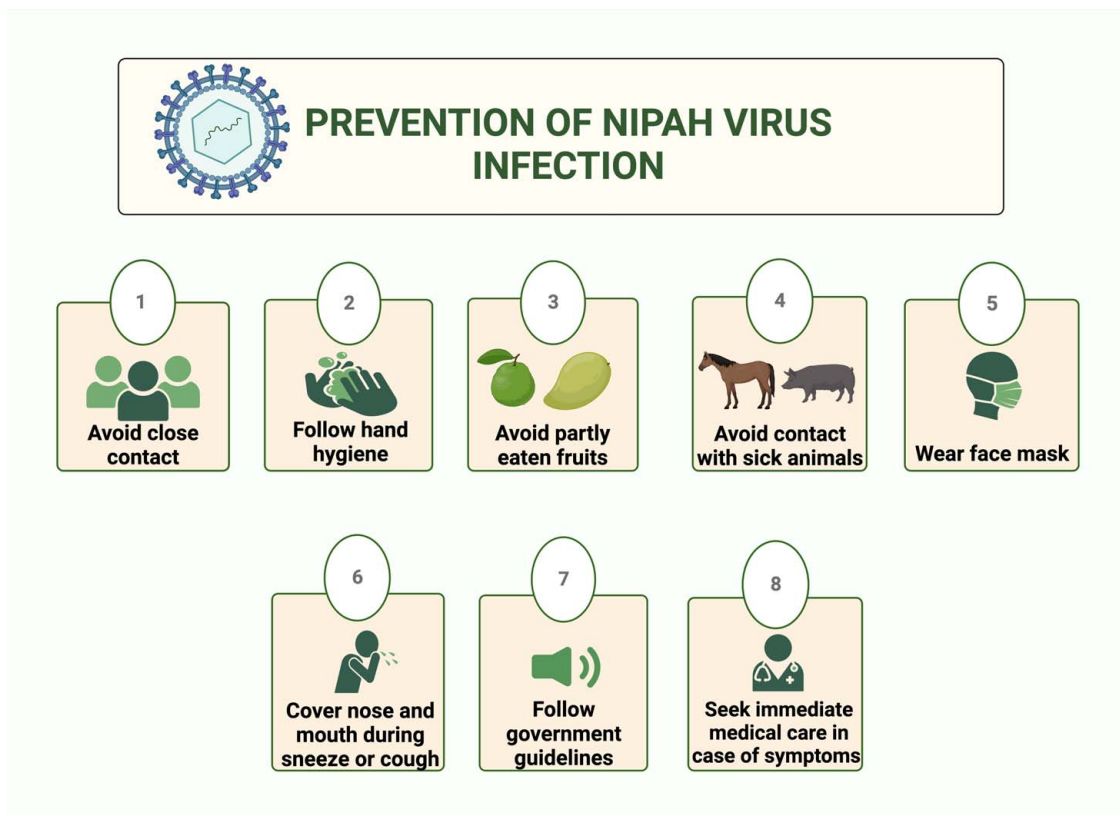


Figure 3. Prevention methods for Nipah virus – The methods include avoiding close contact, following a hygiene protocol, avoiding eating partly eaten fruits, avoiding contact with sick animals, wearing a face mask and covering one’s nose and mouth before sneezing or coughing. Strictly following government guidelines and seeking immediate medical care in case of symptoms is crucial in preventing mortality due to the Nipah virus.

institutions and public transport in the Kozhikode district, which is the centre of the outbreak with the maximum number of affected patients, as a response to curb the spread of this outbreak (Fig. 3). Containment zones have been set up with frequent monitoring of fever and other flu-like illness symptoms, and the public has been urged to wear masks. Furthermore, neighbouring states, such as Tamil Nadu and Karnataka, have been asked to keep watch out for potentially similar outbreaks^[21]. No approved pharmacologic therapy is an effective cure for NiV, with management targeted towards symptomatic management, rehydration, and adequate rest^[5].

The potential development of monoclonal antibodies may aid in the management of NiV. A monoclonal antibody, known as m102.4, has successfully completed phase 1 clinical trials and may prove to be an effective therapeutic option in the future after it demonstrates efficacy during the next phases of clinical trials^[22]. Additionally, remdesivir has shown promise in protecting primates from NiV when used as post-exposure prophylaxis, although studies on humans have not been conducted so far and thus cannot be used as a reliable source for this current outbreak^[23]. Lastly, ribavirin was used to treat a limited number of patients during the early stages of the NiV outbreak in Malaysia, although it has uncertain benefits^[5]. Further research needs to be done for the development of effective vaccines for prophylaxis in areas that are prone to repeated outbreaks^[4]. Pertaining to NiV, focus needs to be put on better control of vectors and the development of effective immunotherapy^[5].

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Consent

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A.V.: conceptualization, methodology, supervision, illustrations, and writing – review and editing; H.J.: supervision, writing – original draft, and writing – review and editing; S.A.S.: methodology, writing – original draft, and writing – review and editing; P.P., A.G., and T.D.: writing – original draft, and writing – review and editing.

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Amogh Verma, ORCID ID: 0000-0003-2499-4874.

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References

- [1] Jain R. Over 700 people tested for Nipah virus after two deaths in India. *Reuters*. Published 13 September 2023. Accessed 21 September 2023. <https://www.reuters.com/world/india/indias-kerala-state-closes-schools-banks-seven-villages-due-nipah-deaths-2023-09-13/>
- [2] World Health Organization. Nipah virus infection – Bangladesh. Accessed 21 September 2023. <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON442>
- [3] The Washington Post. What is Nipah virus? India rushes to contain outbreak. *The Washington Post*. Published 15 September 2023. Accessed 21 September 2023. <https://www.washingtonpost.com/world/2023/09/15/nipah-virus-india-kerala-outbreak/>
- [4] World Health Organization. Nipah virus. Accessed 21 September 2023. <https://www.who.int/news-room/fact-sheets/detail/nipah-virus>
- [5] Centers for Disease Control and Prevention. Nipah Virus (NiV) | CDC. Published 19 October 2022. Accessed 24 October 2023. <https://www.cdc.gov/vhf/nipah/index.html>
- [6] Hunter P. Nipah virus outbreak in India – what you need to know. *The Conversation*. Published 19 September 2023. Accessed 21 September 2023. <http://theconversation.com/nipah-virus-outbreak-in-india-what-you-need-to-know-213692>
- [7] The Indian Express. All you need to know about the Nipah Virus. *The New Indian Express*. Accessed 24 October 2023. <https://www.newindianexpress.com/cities/bengaluru/2023/sep/21/all-you-need-to-know-about-thenipah-virus-2616722.html>
- [8] World Health Organization. Nipah Virus Outbreak in Kerala. Accessed 24 October 2023. <https://www.who.int/southeastasia/outbreaks-and-emergencies/health-emergency-information-risk-assessment/surveillance-and-risk-assessment/nipah-virus-outbreak-in-kerala>
- [9] BBC. Nipah: India's Kerala state tests hundreds after fifth case. *BBC News*. Published 13 September 2023. Accessed 24 October 2023. <https://www.bbc.com/news/world-asia-india-66793836>
- [10] CNN. Nipah virus: India's Kerala rushes to contain a deadly outbreak | CNN. Accessed 24 October 2023. <https://edition.cnn.com/2023/09/14/india/kerala-nipah-virus-india-outbreak-intl-hnk/index.html>
- [11] World Health Organization. Nipah Virus Infection – India. Accessed 24 October 2023. <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON490>
- [12] CIDRAP. Nipah virus outbreak in Bangladesh grows to 11 cases, 8 deaths | CIDRAP. Published 20 February 2023. Accessed 24 October 2023. <https://www.cidrap.umn.edu/nipah/nipah-virus-outbreak-bangladesh-grows-11-cases-8-deaths>
- [13] Mounts AW, Kaur H, Parashar UD, *et al*. A cohort study of health care workers to assess nosocomial transmissibility of Nipah virus, Malaysia, 1999. *J Infect Dis* 2001;183:810–3.
- [14] Chadha MS, Comer JA, Lowe L, *et al*. Nipah virus-associated encephalitis outbreak, Siliguri, India. *Emerg Infect Dis* 2006;12:235–40.
- [15] Ajith Kumar AK, Anoop Kumar AS. Deadly Nipah outbreak in Kerala: lessons learned for the future. *Indian J Crit Care Med* 2018;22:475–6.
- [16] Luby SP, Rahman M, Hossain MJ, *et al*. Foodborne transmission of Nipah virus, Bangladesh. *Emerg Infect Dis* 2006;12:1888–94.
- [17] Epstein JH, Anthony SJ, Islam A, *et al*. Nipah virus dynamics in bats and implications for spillover to humans. *PNAS* 2020;117:29190–201.
- [18] Goh KJ, Tan CT, Chew NK, *et al*. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *N Engl J Med* 2000;342:1229–35.
- [19] Bruno L, Nappo MA, Ferrari L, *et al*. Nipah virus disease: epidemiological, clinical, diagnostic and legislative aspects of this unpredictable emerging zoonosis. *Animals (Basel)* 2022;13:159.
- [20] Mazzola LT, Kelly-Cirino C. Diagnostics for Nipah virus: a zoonotic pathogen endemic to Southeast Asia. *BMJ Glob Health* 2019;4(Suppl 2):e001118.
- [21] Thiagarajan K. Nipah virus: India's Kerala state moves quickly to control fresh outbreak. *BMJ* 2023;382:p2117.
- [22] Centers for Disease Control and Prevention. Treatment | Nipah Virus (NiV) | CDC. Published October 6, 2020. Accessed 24 October 2023. <https://www.cdc.gov/vhf/nipah/treatment/index.html>
- [23] National Institutes of Health. Experimental drug completely effective against Nipah virus infection in monkeys. *National Institutes of Health (NIH)*. Published 29 May 2019. Accessed 24 October 2023. <https://www.nih.gov/news-events/news-releases/experimental-drug-completely-effective-against-nipah-virus-infection-monkeys>