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Short Report

Encephalitis-predominant Nipah virus outbreaks in Kerala, India during 2024

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ABSTRACT

Nipah virus (NiV) is a highly pathogenic zoonotic paramyxovirus with significant public health concern. Since 2018, Kerala, India, has experienced NiV outbreaks with variable clinical manifestations ranging from acute encephalitis syndrome (AES) to acute respiratory distress syndrome (ARDS). Recently, we observed two NiV outbreaks in Malappuram, Kerala, India during 2024, with AES as the predominant clinical manifestation in July and September 2024. Among all close contacts screened no secondary transmission of NiV was observed. The data from NiV outbreaks of Kerala state indicated that AES-predominant outbreaks (2019, 2021, and 2024) had shown no human-to-human transmission compared to ARDS-predominant outbreaks (2001, 2007, 2018, and 2023). Early detection, efficient containment, and improved surveillance were important measures in preventing secondary transmission. The two spill over events of NiV in 2024 reiterates the need for enhancing the surveillance of NiV among ARDS cases for timely case management and containment of the outbreak. In view of this, a network of seventeen Virus Research and Diagnostic Laboratories (VRDLs) was established for surveillance of severe acute respiratory illnesses in West Bengal and Kerala states of India. The continued public health preparedness and community awareness would help to prevent future outbreaks.

Introduction

Nipah virus (NiV), a highly pathogenic zoonotic paramyxovirus, poses a significant public health threat. Primarily transmitted from fruit bats to humans, NiV has emerged in several Asian countries, including Malaysia, Singapore, Bangladesh, India, and the Philippines, with diverse epidemiological patterns and clinical presentations [1]. The potential for NiV to cause widespread epidemics underscores its global health significance.

Clinical presentations of NiV infection exhibit significant variability, encompassing neurological and pulmonary manifestations, often presenting concurrently as acute encephalitis syndrome (AES) and acute respiratory distress syndrome (ARDS) [1]. These severe presentations are associated with high mortality rates, exceeding 70 % in some cases, necessitating rapid and effective public health interventions [2]. The overlapping clinical features with endemic diseases pose significant challenges to differential diagnosis and subsequent control efforts.

Since 2018, six NiV outbreaks/spill over events have been reported in India, including one each in 2018, 2019, 2021, and 2023, and two in 2024, all originating from Kerala [3–7]. Notably, with the exception of the 2018 and 2023 outbreaks, no human-to-human transmission has been observed. The 2019 [5], 2021 [6], and two 2024 outbreaks were isolated single cases with AES-like presentations, demonstrating limited human-to-human transmission. Here, we report two encephalitis-predominant Nipah virus outbreaks in Malappuram district, Kerala, India during 2024. We also aimed to (1) compare the clinical and epidemiological characteristics of AES- and ARDS-predominant NiV outbreaks in Kerala, (2) identify factors influencing transmission dynamics, and (3) examine public health interventions and their effectiveness in outbreak containment.

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Description of NiV cases

The first outbreak in 2024 in Kerala, India was characterized by an unusually rapid onset of AES in a 14-year-old male student from Pandikkad taluka, Malappuram district, Kerala. Presenting with fever since July 10, 2024 with worsening symptoms till July 19 including seizures, and altered sensorium, he sought medical attention at three different healthcare facilities prior to admission to a private hospital in Kozhikode on July 19. The clinical features of the case included rapid-onset meningoencephalitis, myoclonus, and autonomic dysfunction. The brain magnetic resonance imaging (MRI) findings suggestive of cerebellar and pontine infarcts, raised strong suspicion of NiV infection.

On July 20, 2024, the oropharyngeal swab (OPS), urine, and blood samples were collected and referred to ICMR-National Institute of Virology (ICMR-NIV), Pune. The clinical samples were tested using Real-time RT-PCR as described earlier [8]. The assay detected the presence of NiV RNA in OPS (5.4×10^6 copies/ml and EDTA blood (9.5×10^5 copies/ml). The patient succumbed to the infection on July 21 due to severe internal haemorrhage.

To expedite case detection and facilitate rapid containment measures, the ICMR-NIV, Pune deployed a mobile BSL-3 laboratory to the epicenter [7,9]. With the efforts from Kerala State Health Government and team from District Surveillance Unit of Malappuram, a total of 210 contacts [2 high-risk symptomatic, 170 high-risk asymptomatic, 9 low-risk symptomatic, and 29 low-risk asymptomatic] were identified as per the defined case definition and contact tracing protocol as described earlier [4,6]. All the contacts tested negative for NiV RNA.

To investigate potential spill over events, environmental samples, including partially bitten fruits (jackfruit, kanjiram, papaya, hog plum, and mango), and bat droppings from suspected exposure sites, were collected and tested negative for NiV RNA. Furthermore, 52 bats were sampled across four locations in Malappuram district (Vettikkattiri, Pandikkad, Chembrasseri, and Pandallur). While viral RNA was not detected in any bat samples, serological analysis revealed anti-Nipah bat IgG antibodies in 6 bats out of 46 bats (13 %) from Vettikkattiri and Pandikkad (5 km from the index case residence), suggesting ongoing NiV specific IgG antibody circulation within the bat population.

A second NiV outbreak of 2024 was identified in Thiruvali panchayat, Malappuram district, Kerala, approximately 15 km from the July 2024 epicenter. On September 5, a 24-year-old male student, who had returned to Thiruvali from Bangalore, Karnataka, on August 25 following a leg injury, presented with high-grade fever. His condition rapidly deteriorated, with development of vomiting and altered sensorium. He was admitted to a private hospital in Malappuram on September 7 and succumbed to fulminant AES on September 8.

Given recent NiV activity in the region, retrospective testing of the patient's EDTA blood and serum samples at the ICMR-NIV, Pune, confirmed the presence of NiV RNA in Serum (2.2×10^5) and EDTA blood (5.0×10^5). A total of 183 contacts [30 high-risk symptomatic; 150 high-risk asymptomatic; 2 low-risk symptomatic; and 1 low-risk asymptomatic] were identified and tested negative for NiV RNA. Despite extensive investigations, a definitive epidemiological link or cause of spill over events remains elusive in all Indian NiV outbreaks from Kerala, including those of 2024. Next generation sequencing of clinical specimens of both the outbreaks of 2024 shown highest homology with NiV I-genotype reported earlier during 2018, 2019, and 2023 nipah outbreaks from Kerala.

Discussion

Indian NiV outbreaks exhibit diverse clinical presentations, with a spectrum ranging from AES to ARDS and even mixed clinical presentation significantly influencing outbreak dynamics. The 2001 Siliguri, West Bengal, India outbreak, the largest recorded with 66 cases and 45 fatalities, demonstrated significant human-to-human transmission initiated by an index case presenting with ARDS with AES [10]. The 2007 Nadia, West Bengal, India of NiV outbreak, involving five cases [4 cases within a single family, and a healthcare worker] resulted in 100 % mortality. All cases, including the index case, presented with ARDS with subsequent development of AES, leading to secondary transmission from index case [11].

The 2018 Kozhikode, Kerala, outbreak [23 cases (laboratory confirmed [n=18] and suspected [n=5]), 21 fatalities] exhibited a spectrum of clinical presentations, including ARDS, ARDS with AES, and isolated AES cases [3,4]. The index case, presenting with fulminant ARDS, led to the emergence of 20 secondary cases. The 2023 Kozhikode outbreak, with six cases and two fatalities, also originated from an index case with ARDS presentation [7]. (Table 1). Albeit, the 2019 [5], 2021 [6] and 2024 outbreaks in Kerala, each involving a single case, were characterized by isolated AES presentations without respiratory involvement (Table 1).

Nosocomial transmission of NiV poses a significant risk, particularly among healthcare workers and bystanders exposed to respiratory secretions from patients with ARDS. The outbreaks of 2001, 2007, 2018, and 2023 serve as stark reminders of the heightened transmissibility associated with ARDS manifestations. The characteristic coughing and other respiratory symptoms in ARDS patients generate virus-laden aerosols, which, due to their smaller particle size, can travel greater distances and remain suspended in the air for extended periods, increasing the risk of inhalation and subsequent infection [12]. This contrasts sharply with outbreaks where AES predominates, as seen in 2019, 2021, and 2024. Furthermore, the viral load and shedding patterns in AES cases may differ, potentially contributing to reduced transmissibility.

Analysis of NiV outbreaks in India reveals that the predominance of encephalitis as the primary clinical manifestation among index cases may, paradoxically, lessen the potential for widespread human-to-human transmission. Furthermore, the neurological symptoms associated with encephalitis, such as altered mental status and seizures with signs of myoclonus and autonomous dysfunction led to early identification by physicians considering the previous experiences with NiV outbreaks in Kerala. This may also lead to earlier hospitalization and isolation of these patients, inadvertently limiting their contact with susceptible individuals during the peak of their infectiousness. In contrast, individuals with respiratory presentations, particularly those with cough followed by ARDS, may remain undiagnosed and in the community for a longer period, potentially shedding higher amounts of virus and contributing to more extensive transmission. The lower transmissibility observed in AES-predominant cases may be attributed to viral tropism, immune response variations, and behavioral factors, such as the reduced need for close-contact patient care compared to ARDS cases, which often involve aerosol-generating procedures.

While continued vigilance and surveillance for all NiV cases remain paramount, a heightened focus on the rapid identification and isolation of individuals presenting with respiratory distress, especially in regions with a history of NiV outbreaks, is critical. In response to the experiences from these outbreaks, India has intensified NiV surveillance in West Bengal and Kerala, establishing a network of ten and seven trained Virus Research and Diagnostic Laboratories (VRDLs), respectively. Since November 2024, these laboratories have initiated screening for NiV infection among cases of severe acute respiratory illness (SARI) negative for other common endemic viral respiratory pathogens. This targeted approach helps to identify potential NiV cases early, even when they might be masked by similar illnesses. The focus on SARI cases is particularly important given the heightened transmissibility of NiV associated with ARDS presentations. Early detection through this surveillance network would allow

Table-1
Clinico-epidemiological, genomic characterization and bat positivity observed during the Nipah virus outbreaks in India [2001–2024].

Year	Month	Location	Total cases	Deaths [CFR]	Primary Presentation of Index case	Age [Index case]	Gender [Index case]	Occupation of Index case	Number of secondary cases infected by index case	POD of detection of Index case	NiV Viral RNA copies/ml of index case	Close Contacts screened	Asymptomatic/ Subclinical infections observed	Outcome of Index case [Survived/ Died]	Duration of outbreak [cases detection]	Genomic characterization of the outbreak sequences [Accession number]	Bat positivity
2001	January-February	Siliguri district, West Bengal	66	45 [68.18 %]	Predominant ARDS with AES	[a]No data available	Male	[a]No data available	Probable 11 secondary cases followed by tertiary cases	[a]No data available	[a]No data available	[a]No data available	[a]No data available	Died	January 31-February 23, 2001	!Partial N and M gene nucleotide sequence of NiV matched 97.5 % and 99 % respectively with Bangladesh 2004 strain	Not available
2007	April	Nadia district, West Bengal	5	5 [100 %]	Predominant ARDS with AES	35 year	Male	Farmer [used to consume date palm sap]	4	[a]No data available	[a]No data available	[a]No data available	[a]No data available	Died	April 9–28, 2007	99.2 % Nucleotide and 99.8 % Amino Acid identity with the Bangladesh 2004 isolate [FJ513078]	Not available [Bat roosting observed near index case]
2018	May	Kozhikode district, Kerala	23	21 [91.3 %]	Predominant ARDS with AES	27 years	Male	Laborer	20 [additional 3 are tertiary cases]	[a]No data available	[a]No data available	2642	• 2 [Anti-Nipah IgM and IgG positive][b] • 1 [Anti-Nipah IgM][b]	Died	May 2–29, 2018	96.15 % similarity to Bangladesh strain [MH396625, MH523640, MH523641, MH523642]	NiV RNA positivity 13/52 (25 %)
2019	May-June	Ernakulum district, Kerala	1	0	AES	21 year	Male	Student	0	10 days	• Urine [1.6×10^4]	330	0	Survived	May 30, 2019	99.70 % identical to the 2018 outbreak sequence [OR130496]	Anti-NiV bat IgG antibodies were detected in 12/58 [20.68 %]
2021	August-September	Kozhikode district, Kerala	1	1 [100 %]	AES	12 year	Male	Student	0	5 days	• EDTA blood [7×10^5] • Bronchial wash [3.5×10^4] • ET secretion [1.1×10^{-7}] • CSF [3.5×10^4]	64	0	Died	August 29, 2021	99.62 % identical to the 2018 outbreak sequence [I genotype] [OM135495]	Anti-NiV bat IgG antibodies were detected in 8/38 *Pteropus* [21 %] and in 20/63 [31.7 %] *Rousettus* spp
2023	August-September	Kozhikode district, Kerala	6	2 [33.33%]	Predominant ARDS with AES	45 year	Male	Not Known	5	5 days	• OPS [7.2×10^{-6}]	253	0	Died	August 25-September 11, 2023	Sequences belonged to I genotype identical to 2018 and 2019 outbreak [OR820506]	Anti-NiV bat IgG antibodies were detected in 31/110 [28.18 %]
2024	July	Malappuram district, Kerala	1	1 [100 %]	AES	14 year	Male	Student	0	10 days	• OPS [5.4×10^6] • EDTA blood [9.5×10^5]	210	0	Died	July 10, 2024	Sequences belonged to I genotype identical to 2018, 2019 and 2023	Anti-NiV bat IgG antibodies were detected in 6/46 [13 %]

(*continued on next page*)

Table-1 (*continued*)

Year	Month	Location	Total cases	Deaths [CFR]	Primary Presentation of Index case	Age [Index case]	Gender [Index case]	Occupation of Index case	Number of secondary cases infected by index case	POD of detection of Index case	NiV Viral RNA copies/ml of index case	Close Contacts screened	Asymptomatic/ Subclinical infections observed	Outcome of Index case [Survived/ Died]	Duration of outbreak [cases detection]	Genomic characterization of the outbreak sequences [Accession number]	Bat positivity
2024	September	Malappuram district, Kerala	1	1 [100 %]	AES	24 year	Male	Student	0	4 days	• Serum [2.2×10^5] • EDTA blood [5.0×10^5]	183	0	Died	September 5, 2024	Sequences belonged to I genotype identical to 2018, 2019 and 2023	Not done as it was near the July 2024 epicenter area

CFR, Case Fatality Ratio; AES, Acute Encephalitis Syndrome; ARDS, Acute Respiratory Distress Syndrome; POD, Post Onset Day of illness; OPS, Oropharyngeal Swabs; NPS, Nasopharyngeal swabs.

[a] No data or specimens were obtainable for the index case, as the outbreak was identified post-mortem and subsequent to the onset of secondary transmission.

[b] Ref. [13].

for rapid isolation of suspected NiV cases, preventing further spread within healthcare facilities and the community. The availability of MBSL-3 laboratory represents a new exemplar in India's frontline combat against highly infectious pathogen outbreaks and can be deployed as an essential component of the outbreak control effort. The Kerala government has launched the 'No Nipah Campaign' to educate the public about probable sources of infection and transmission dynamics, as well as to encourage behavioral change in order to minimize human-animal interaction. Additionally, the improvement in the hospital infection control practices is critical to reduce the onward transmission of NiV as observed in earlier outbreaks in India. While our findings are based on NiV outbreaks in Kerala and West Bengal, similar patterns may or may not be observed in other regions of the country due to variations in ecological factors, healthcare infrastructure, and public health responses. Further research exploring the specific viral and host factors that contribute to these different clinical presentations and their respective transmissibility is warranted.

Ethical approval

The study was approved by the Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project 'Virus isolation, characterization and development of diagnostics assay for high-risk pathogens' [MCI2305].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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