https://doi.org/10.1038/s44360-025-00014-9

Research and development priorities for Nipah virus outbreak preparedness

Michael S. Avumegah, Anthony Griffiths, Christina F. Spiropoulou, Giada Mattiuzzo, Emma M. Bentley, Tahmina Shirin, Sharmin Sultana, Valentina Bernasconi & Ali Azizi

Standardized clinical assays, diagnostic assays and, ultimately, a vaccine are needed to prepare for future Nipah virus outbreaks.

Nipah virus (NiV) is a member of the family *Paramyxoviridae*, in the genus *Henipavirus*. It is a zoonotic virus – a virus that naturally infects animal hosts but can infect humans[1]. NiV is one of the priority pathogens in the Coalition for Epidemic Preparedness Innovations (CEPI) priority disease portfolio, owing to its high lethality, outbreak potential and the absence of licensed vaccines. CEPI has funded NiV vaccine development since 2018, and continues to make substantial investments in enabling scientific projects, including the production of international standards for NiV antibodies, assay development and epidemiological studies. In 2023, CEPI convened a diverse group of experts and stakeholders in Kuala Lumpur, Malaysia. The meeting brought together 64 NiV experts from over 25 institutions, including the US National Institutes of Health, UK Medicines and Healthcare products Regulatory Agency (MHRA), PATH, the University of Oxford, Moderna, the Ministry of Health in Malaysia, and many others. The discussions covered a wide range of topics, including CEPI's NiV strategy, clinical assays, disease epidemiology, medical interventions and emerging henipaviruses. In this Comment, we summarize the key discussion points, and focus on the experiences of countries affected by NiV outbreaks and highlight critical research gaps and opportunities. Additional insights were gained from a tabletop exercise that examined global readiness to a highly transmissible Nipah-like virus using currently available technologies and resources.

NiV outbreak in Malaysia, Bangladesh and India

Malaysia's response to the first NiV outbreak in 1998 exemplified a holistic, multisectoral approach to outbreak containment and public health coordination. The outbreak resulted in 265 cases of acute encephalitis in humans, and 105 fatalities. It also had a considerable economic effect, as over a million pigs were culled to help to control the spread of the disease. Initially, the disease in pigs and farmers was thought to be African swine fever and Japanese encephalitis, respectively. The Malaysian government proactively implemented measures, such as vector control and vaccination, to combat Japanese encephalitis. However, these efforts were unsuccessful, as case numbers continued to rise and the outbreak spread to Singapore in March 1999. Many healthcare workers suspected that this could have been a novel virus, as the symptoms were not typical of Japanese encephalitis. In addition, many of the patients who reported cases had been vaccinated against Japanese encephalitis. The isolation of the aetiological agent NiV from the cerebrospinal fluid of some patients was the turning point that led to successful outbreak containment.

The first known NiV outbreak in Bangladesh occurred in 2001 in the Meherpur district, located in the western part of the country. NiV outbreaks in the country are typically linked to the consumption of raw date palm sap contaminated with NiV. The largest outbreak recorded to date was in 2004, which had 67 confirmed cases[2]. Since then, Bangladesh reports cases nearly every year. In 2006, the government established an active NiV surveillance system as a control measure, through the Institute of Epidemiology, Disease Control and Research in collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) and technical support from the US Centers for Disease Control and Prevention. The NiV outbreak that occurred in 2023 recorded 14 cases. From 2001 to 2024, a total of 343 NiV cases were reported (Fig. 1), which resulted in 245 deaths.

India reported its first NiV outbreak in 2001 in Siliguri, West Bengal[3]. Initially, the outbreak was believed to be caused by the measles virus. Nearly five years later, the samples collected were retrospectively tested, and NiV infection was confirmed. Since then, 4 confirmed NiV outbreaks have occurred, which have resulted in a total of 90 recorded cases between 2007 and 2021. The 2007 NiV outbreak took place in West Bengal state, near the Bangladesh border. Bat surveys in West Bengal and nearby Assam state revealed the presence of NiV antigens and antibodies in bats of *Pteropus* sp. Drawing from the Malaysia experience, 1,113 pigs were screened for NiV antibodies, but all were found to be negative.

The subsequent outbreaks (2018, 2019 and 2021) occurred in a geographically distant location in the southernmost state of the country, Kerala. The outbreaks in India have been linked to infected bats in endemic areas. In response to the repeated outbreaks, the Indian Council of Medical Research initiated a nationwide bat survey to better understand the distribution of NiV across the country. Although the survey is still ongoing, it has already detected the presence of antibodies in populations from multiple states.

Neurological disease and animal model development

Research studies discussed at the CEPI meeting emphasized the need for further investigation into NiV-related neurological disease. Although neurological diseases have been observed in animal models challenged with NiV[4,5], current preclinical vaccine studies are primarily focused on lethal respiratory disease end points. This hampers a full understanding of effectiveness of countermeasures to prevent or treat neuropathology associated with NiV disease in humans. Neurological disease is not only a major cause of death but is also associated with long-term sequelae in survivors of NiV disease[6]. Research studies have also shown that NiV may persist in the brain in humans and in several animal models, including non-human primates and porcine models. In a hamster disease model, NiV can enter the central nervous system within 4 days of intranasal inoculation. Postmortem analysis of encephalitis cases from the Malaysia outbreak corroborates the neuroinvasion seen in animal models[4,5]. Owing to the sporadic nature of NiV outbreaks, vaccine developers have faced challenges in conducting traditional

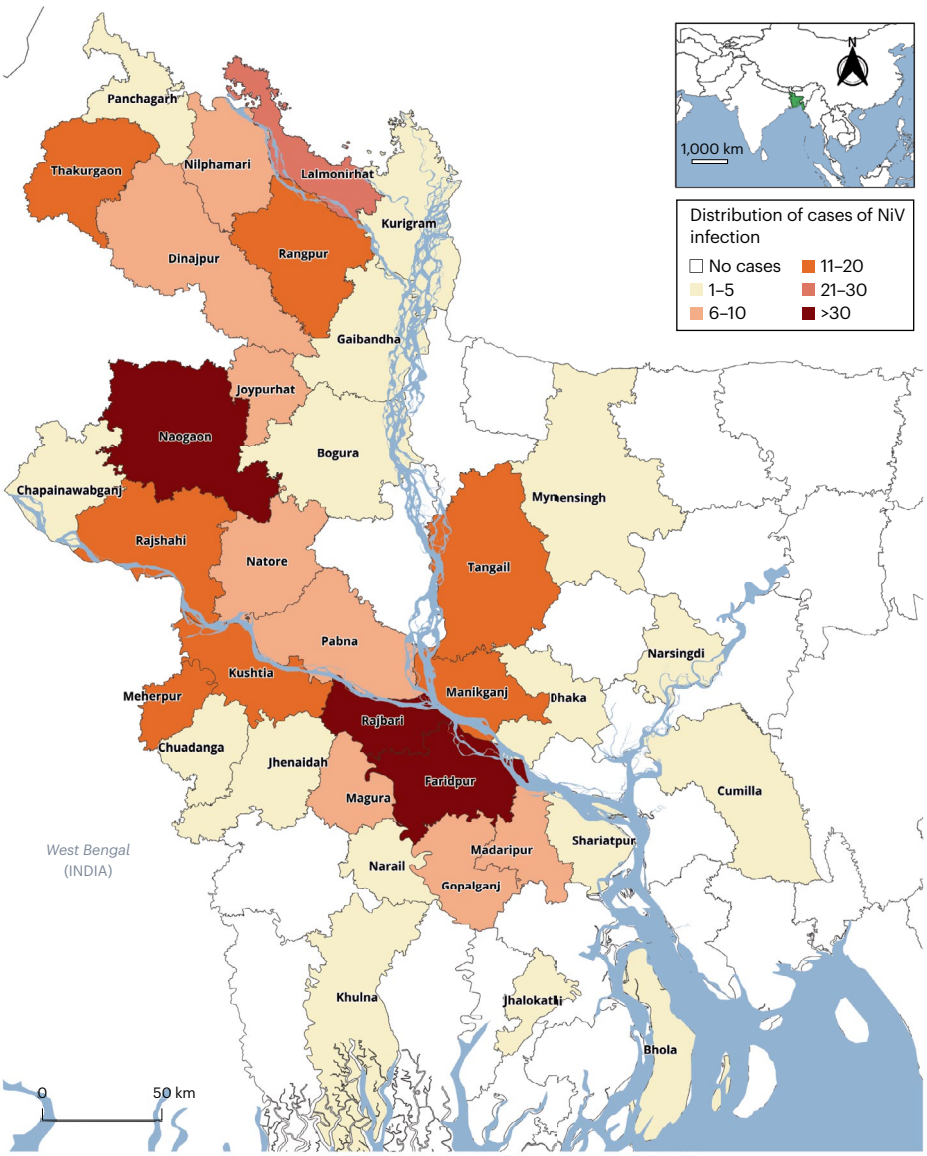

Fig. 1 | Cases of NiV infection in Bangladesh. The map presents an epidemiological analysis to support public health planning by visualizing the spatial distribution of reported cases. Colour-coded districts highlight high-risk areas. Data are from 2001 to 2025. Credit: Map preparation: Dr. Maruf Ahmed Bhuiyan, Lab research Officer, Characterizing the Epidemiological Diversity of Nipah Strains from Bangladesh, IEDCR and Dr Mintu Chowdhury Project Coordinator, Characterizing the Epidemiological Diversity of Nipah Strains from Bangladesh, IEDCR.

efficacy clinical trials and securing subsequent vaccine licensure. Through its Preclinical Model Network, CEPI is currently funding the development of NiV animal models at the National Emerging Infectious Diseases Laboratories to support NiV vaccine projects. Additionally, the CEPI Centralized Laboratory Network also is providing support for the development of standardized NiV validated assays to support clinical trials[7,8].

Reference standards and diagnostics

A readily available World Health Organization (WHO) International Standard for an anti-NiV antibody has been facilitated by CEPI through partnership with ICDDR, B, University of Malaya and the MHRA[9]. The antibody standard available from the NIBSC catalogue[10] is a crucial tool to support vaccine developers, and part of CEPI's broader efforts to strengthen the NiV research ecosystem through enabling scientific projects. Similarly, NiV diagnostics are crucial for disease detection and surveillance, especially in monitoring outbreaks. Although there are commercially available nucleic acid tests and serological assays, only a few have independent performance data and regulatory approval. Most tests used in national reference laboratories where the disease is endemic are in-house assays, which are not easily implementable or scalable for response to new outbreaks in new areas. There is a near-point-of-care nucleic acid test available that has been used in the field for outbreak responses in India, but diagnostics suitable for use in

district laboratories and private healthcare facilities are lacking. There is an urgent need to improve the limited availability of commercial or standardized assays with regulatory approval for NiV disease. This includes developing diagnostics suitable for decentralized testing to enable rapid case detection in lower-tier or community settings. These tests must be highly specific, sensitive, affordable and safe. In addition, enhanced surveillance efforts are also required.

Correlates of protection

Limited information is available on which aspects of the human immune response to acute NiV infection correlate with survival. Most studies have focused on humoral immune responses and the induction of neutralizing antibodies in survivors of NiV disease. To date, only one longitudinal study on acute NiV human infection has been conducted, which involved two survivors during the Kerala outbreak in 2018 (ref. 11). This study indicated strong induction of activated CD8 T cell responses, followed by the presence of immunoglobulin M and immunoglobulin G antibody responses. Induction of both cell-mediated and humoral immune responses to NiV has also been reported in infected pigs[12] and experimentally infected non-human primates[13]. Correlates of protection of disease have not been well defined. The prevailing hypothesis is that the presence of neutralizing antibodies is key to the correlates of protection for NiV. This is largely based on the successful use of neutralizing monoclonal antibodies as therapeutic agents and survival of all vaccinated, and then challenged, animals that had developed neutralizing antibodies at the time of challenge. However, neutralizing antibodies do not necessarily have to be detectable at the time of virus exposure to confer protection. This has been shown in a number of studies in which African green monkeys — which were challenged only 7 or 14 days after vaccination — had no detectable neutralizing antibodies at the time of challenge, but had a rapid antibody rise after the challenge that probably mitigated the infection[14,15]. Additionally, Fc-mediated effector mechanisms, including antibody-dependent cellular phagocytosis and antibody-dependent complement deposition, have been implicated in conferring protection early after vaccination. Despite this accumulating evidence, further studies in animal models and human NiV infections are still required. It appears that comparable results between assay platforms (authentic virus neutralization assays and pseudotyped virus-based neutralization tests) are required to gain confidence in the results from the preclinical and clinical studies on vaccine-induced immunity. The availability and use of a WHO International Standard for NiV antibodies and validated methods could harmonize results between assays and laboratories, and enhance progress towards defining correlates of protection.

Gaps and opportunities

Research presentations and the tabletop exercise during the CEPI meeting in Malaysia in 2023 showed that, although progress has been made in understanding the mode of NiV transmission to humans, much of NiV epidemiology remains unclear and further research is required to fully elucidate the natural history of transmission. During NiV outbreaks, the focus has been on identifying and isolating symptomatic cases. However, limited attention has been given to asymptomatic NiV cases, which may have the potential to drive human-to-human transmission. These cases are difficult to identify, which highlights the need for rapid, easy-to-use, point-of-care diagnostic tests. Such tests should be readily available in rural areas of endemic countries to screen both symptomatic patients and close contacts. There is also a need for longitudinal studies and surveillance in endemic countries to better understand the plausible modes of transmission and to initiate ongoing bat surveillance to monitor virus activity. This could help to estimate risk and prevent future spillovers. Furthermore, a better understanding of the current NiV strains circulating in bats, as well as the characteristics of those that spillover into humans, is required. Although some comparatives studies have been conducted on the NiV Bangladesh and Malaysia strains, NiV India strain has yet to be incorporated into such studies.

Conclusion

NiV is a priority pathogen for CEPI and is listed in the WHO Research and Development Blueprint 2018 (ref. 16) as an epidemic threat that requires urgent action, with a fatality rate of 40–70% in recorded outbreaks and no vaccines available. CEPI continues to spearhead efforts in supporting the development of NiV countermeasures, diagnostics and vaccine platforms. By convening key stakeholders, CEPI is actively driving discussions on use cases, target product profiles and sustainable financing models. In addition, CEPI has allocated funding to support scientific projects aimed at establishing NiV standards and advancing assay development to facilitate vaccine development. Furthermore, CEPI (through its collaboration with several partners) is exploring the correlates of protection in NiV to accelerate vaccine development in alignment with CEPI's 100 Days Mission.

Despite these critical advancements, much more work is needed to create a comprehensive, global strategy for the prevention of NiV outbreaks and to mitigate the risk of a potential NiV pandemic. This ongoing work is essential to ensuring that the global health community is prepared to respond swiftly and effectively to future NiV threats.

Michael S. Avumegah[1], Anthony Griffiths[2], Christina F. Spiropoulou[3], Giada Mattiuzzo[4], Emma M. Bentley[4], Tahmina Shirin[5], Sharmin Sultana[5], Valentina Bernasconi[6] & Ali Azizi[7] ✉

[1]Coalition for Epidemic Preparedness Innovations (CEPI), London, UK. [2]Laboratory for Infectious Disease Research, Bond Life Sciences Center, University of Missouri, Columbia, MO, USA. [3]Viral Special Pathogens Branch, Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA. [4]Medicines and Healthcare products Regulatory Agency (MHRA), South Mimms, UK. [5]Institute of Epidemiology Disease Control and Research, Dhaka, Bangladesh. [6]Coalition for Epidemic Preparedness Innovations (CEPI), Oslo, Norway. [7]Coalition for Epidemic Preparedness Innovations (CEPI), Washington, DC, USA.
✉e-mail: ali.azizi@cepi.net

Published online: 15 January 2026

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Acknowledgements
The authors thank colleagues at CEPI, as well as partners and collaborators, for their contributions to our NiV meeting and projects. Special thanks to D. Emperador, W.-Y. Chan, P. D. Yadav, R. Kenneil, A. Isaacs, R. Mahbubur, L.-Y. Chang, R. Nichols, J. Fusco and R. Jarman. We also thank M. A. Bhuiyan and M. Chowdhury from the Institute of Epidemiology, Disease Control and Research (IEDCR) for providing the images for this Comment.

Competing interests
The authors declare no competing interests.