Title: Nipah virus disease at 25: what can we do to improve patient care?

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Summary:

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This year marks the 25th anniversary of the first detected outbreak of Nipah virus (NiV) disease. Despite being a priority pathogen in the World Health Organization Research and Development blueprint, the disease still carries high mortality, unchangfed since the first reported outbreaks. Whilst candidate vaccines exist, there have been insufficient investments into developing new therapeutics. NiV disease illustrates the typical “market failure” of medicine development for a high-consequences pathogen: a relatively low number of cases affecting economically-disadvantaged populations in low-resource countries, and unpredictable outbreaks do not make an attractive “business case” – a situation compounded by methodological challenges in clinical trial design. Clearly, NiV therapeutics development will not be motivated by commercial interest. We, therefore, propose a regionally-led, patient- and public health-centred, end-to-end framework that clearly articulates a public health vision and a roadmap for research, development, manufacturing and access towards the ultimate goal of improving patient outcomes. This framework includes co-creating a regulatory-compliant, clinically-meaningful, and context-specific clinical development plan and establishing quality standards in clinical care and research capabilities at sites where the disease occurs. Ultimately, the success of this approach will be measured by the availability and accessibility of improved treatments in affected communities and a reduced mortality.

Text:

1 Introduction

The detection of an increase in Mpox virus cases in West Africa from 2017 should have served as a warning sign of potential outbreaks elsewhere. However, it was not until the multi-country outbreak in 2022, which prompted the World Health Organization (WHO) to declare a public health emergency of international concern (PHEIC), that the disease received significant global attention[1]. This outbreak highlighted two frustrating issues in global health that must be corrected: first, high-consequence infectious diseases receive attention only when they affect high-income countries; second, even when interventions are available, they may not reach those who need them most [2,3], but are instead stockpiled and reserved for use in high-income countries, as observed also in Ebola[3] and the COVID-19 pandemic[4].

We must avoid the same pattern being repeated with Nipah virus (NiV) disease. Recurrent outbreaks in economically-disadvantaged rural communities in South or South East Asia have so far resulted in limited action to understand and mitigate the disease. But we should not wait until a more extensive outbreak threatens or affects wealthier countries before acting towards developing better treatment options, and deploy them when and where needed.

Nipah is a highly lethal zoonotic paramyxovirus that can infect humans through contact with infected bats, pigs, or humans, or by consuming contaminated raw date palm sap[5,6]. It causes a rapidly progressive illness that affects the respiratory and central nervous systems, including respiratory distress and encephalitis, with a very high case-fatality ratio. Since its discovery in 1998/1999 in Malaysia and Singapore, NiV has caused sporadic outbreaks in Bangladesh, India, and the Philippines, with concerns about future outbreaks in other regions where *Pteropus* bats, the zoonotic reservoir of NiV, are found (Table 1). The wide geographic distribution of these bats across Africa, South Asia, and Oceania, combined with the virus's capacity for person-to-person transmission and evidence of ongoing viral evolution, underscores the potential for larger epidemics[7,8 9,10].

In 2018 the WHO listed NiV as a priority pathogen for urgent research and development (R&D) and produced a roadmap to address the research needs for Nipah, including developing diagnostics, therapeutics and vaccines[11,12]. Encouragingly, the Coalition for Epidemic Preparedness Innovations (CEPI), primarily funded by public and philanthropic organizations with some contributions from the private sector, has invested in the development of multiple vaccine candidates for NiV and notable progress has been made, withat least two candidates having reached in-human (Phase I) clinical trials [13]. In contrast, investment and progress in therapeutics is less advanced., Currently, there are no approved vaccine or therapies available for NiV disease.

2 Clinical outcomes in patients with Nipah virus disease

NiV mortality varies widely from 9% in Singapore (the only high-income country reporting NiV cases) to 100% in some transmission clusters [14,15], and has remained essentially unchanged from the initial outbreaks of NiV in Malaysia (40%), Bangladesh (70%), and India (68%)[16,17] (Table 1). The reasons for this difference, which requires further investigation, are presumably multifaceted and may include variations in the infecting NiV strains (NiV M vs, NiV B) [10,18], route of infection (respiratory vs gastrointestinal) [5,19], patient characteristics, and access to adequate supportive care. In 2023, Bangladesh experienced the largest Nipah outbreak since 2015, with a case-fatality ratio of 71% with 10 deaths out of 14 reported cases so far [20]. Furthermore, a new outbreak has surfaced in Kozhikode district, Kerala, India, with six confirmed cases including two fatalities to date [21]. The continued high mortality is likely a result of several factors, including delays in diagnosis, absence of specific therapies, and lack of effective supportive care.

The lack of laboratory infrastructure and diagnostic capabilities in rural areas where NiV outbreaks occur creates challenges in early diagnosis, thereby impeding timely treatment [22]. Additionally, the nonspecific initial signs and symptoms of NiV infection, combined with the lack of point-of-care rapid diagnostic tests, often lead to delays in diagnosis in endemic areas where many patients present with encephalitis of various aetiologies. Distinguishing Nipah virus infection, representing only about 3% of all encephalitis cases in Bangladesh, from other causes of encephalitis is, therefore, challenging [23-25].

At present, the clinical management of encephalitis patients, including those whose illness is caused by NiV, is primarily supportive [26]. This involves administration of oxygen, fluids, and nutritional support, and resuscitation as needed, alongside symptomatic treatment, including the use of antipyretics, anticonvulsants, treatment for raised intracranial pressure, hypoglycaemia, and shock. Empiric treatment is typically initiated with antibiotics (intravenous ceftriaxone), antivirals (intravenous acyclovir) and steroids[26]. Patients with worsening conditions such as a deteriorating level of consciousness, uncontrolled seizures, hemodynamic instability, and multiorgan failure are assessed for transfer to an intensive care unit (ICU) and/or higher centres[26]. Improving patient outcomes in ongoing NiV outbreaks remains a significant challenge due to the lack of standardized supportive care available to patients in endemic areas, including timely access to ICUs. Advancing knowledge to guide clinical care and improve outcomes for isolated NiV cases and small clusters will also be good preparation for a potential larger epidemic in the future.

3 Why so little progress in improving patient outcomes?

There are several critical barriers to identifying and evaluating therapeutic interventions for NiV disease.

3.1 Epidemiological challenges:

The disease is characterized by low caseloads even in endemic areas, with sporadic cases and unpredictable outbreaks in terms of location, size, and timing [27]. This presents enormous methodological and operational challenges for clinical trials. Bangladesh, where the epidemiology of NiV is well understood, and which has experienced the highest number of reported outbreaks, is a suitable site for potential Nipah therapeutic trials [6]. However, even in Bangladesh, NiV cases remain infrequent and geographically dispersed, with an average of 14 confirmed cases reported each year [28]. This makes traditional phase 3 efficacy trials impossible to conduct in the current epidemiological context.

3.2 Operational challenges:

NiV disease outbreaks occur in areas with limited research infrastructure and clinical research capacity, leading to limited understanding of the clinical characteristics and outcomes of the disease, and hindering the implementation of effective clinical trials. In addition, the lack of laboratory and clinical infrastructure in rural communities in Bangladesh and India creates challenges for timely diagnosis and enrolment into research studies [22]. Moreover, the lack of Biosafety level 4 (BSL-4) facilities – of which there are none in Bangladesh – to manage the high-level biocontainment requirements for handling NiV, impedes locally-led research on disease pathogenesis and the in-vitro and in-vivo evaluation of therapeutics.

In Bangladesh, where NiV is endemic, surveillance relies on a central laboratory located in the capital city, Dhaka. As a result, confirming a diagnosis can take several days or weeks [25]. Therefore, the development of rapid, ideally point-of-care, diagnostic tests and improved laboratory infrastructure and diagnostic capabilities is critical for the accurate diagnosis and timely treatment of patients, as well as the prevention of disease spread.

3.3 Market and policy challenges:

Apart from one inconclusive open-label trial with ribavirin during the Malaysian outbreak and a Phase 1 study with the monoclonal antibody m102.4 conducted on healthy volunteers in Australia, no other human clinical trials have been conducted to date for any potential NiV therapeutic candidates [29,30].

This lack of progress in therapeutic development reflects both a market failure and a global health policy failure. The small numbers of NiV cases in countries unable to provide the substantial financial resources required to invest in the R&D process or to pay for stockpiling therapeutics, means there is no financial incentive to drive profit-driven private sector investment. Equally there have been few public investments made both at the local level and globally to support the discovery and development of new therapeutics and/or attract private sector actors into the types of public-private partnerships that have pushed drugs through the R&D pipeline in other disease areas, ideally creating affordable products and a sustainable local market [31].

4 Way forward:

There are potential therapeutic candidates for henipaviruses, including NiV, currently progressing through the R&D pipeline including at least eight small molecules and four monoclonal antibodies, which are mainly in the preclinical stage[32] (Table 2). Only the monoclonal antibody m102·4 has phase 1 data available, while both m102·4 and ribavirin have been used on a compassionate basis during outbreaks[29]. To effectively evaluate potential interventions for improving patient outcomes in light of the aforementioned challenges, a coordinated, public health-focused approach must be adopted that maximizes the chance of identifying and progressing the best therapeutic options in a timely way, that emphasizes fairness, transparency, and equitable access to interventions for NiV-affected communities [4 33].

We propose a model similar to the West Africa Lasa fever Consortium (WALC) to generate essential elements of a pathway to develop and make available new treatments to those in need [33]. This model includes laying out a clinical development plan that is regulatory-compliant, clinically-meaningful, and context-specific, as well as strengthening research sites' capacity to meet regulatory quality standards (good clinical practices and good clinical laboratory practices) and ensuring good participatory practice for trials (GPP) [34]. Moreover, the model recognizes the need for involving key stakeholders both in NiV-endemic countries and internationally, and establish an end-to-end partnership and financing structure in which all actors commit to the collective end goal of equitable access to effective treatments. The key aspects of this plan are summarised below.

4.1 Enhanced clinical epidemiology:

A key clinical difference between NiV outbreaks is that, despite a consistently high proportion of cases presenting with encephalitis (~97%) across all outbreaks, in Malaysia, fewer cases had respiratory symptoms (14-29%) [14], compared to Bangladesh (62-69%)[15] and India (51%)[35], where it is sometimes leading to acute respiratory distress syndrome[15]. Notably, two out of eleven patients in the Malaysian outbreak among abattoir workers in Singapore presented with pneumonia without encephalitis [16]. Similarly, in the current Kerala outbreak in India, reported cases also had pulmonary presentation [21].

The variation in pulmonary involvement likely owes to differences in NiV strains and/or in the route of infection. Experimental evidence indicates that NiV-B replicates more efficiently in human tracheal and bronchial epithelium than NiV-M[36,37]. It is unclear whether early ribavirin treatment during the Malaysian outbreak might have had a role in controlling virus replication in the lung – thus accounting for lower mortality [30,38]. To gain a comprehensive understanding of the clinical characteristics and natural history of NiV disease, including both encephalitis and pulmonary presentations, prospective observational clinical research is essential. This can form the foundation for developing, standardized clinical trial methodologies.

This enhanced clinical epidemiology study should also document current clinical care practices to identify gaps and inform the development of context-specific standard of care guidelines. During the Malaysian outbreak in 1998-99, 10 out of 11 patients cared for in a Singapore hospital survived[39], suggesting that improving elements of supportive care can significantly improve patient outcomes.

4.2 Defining use cases and target product profile for NiV therapeutics:

Developing safe and effective therapeutic agents to treat acute NiV disease and its acceptance by the end-users- clinicians and patients is crucial for improving survival rates and reducing associated morbidity and long-term disability. However, to design and select therapeutics that achieve these objectives, we need to define use-cases and a clear criterion for down-selection and prioritization of candidate products for clinical trials.

Defining use-cases of potential therapeutic options as illustrated in Figure 1 is essential to support the development of the target product profile (TPP) that serves as a guide for drug developers and other actors in the clinical development pathway, indicating the necessary and suitable characteristics for future therapeutic candidates after consultation with key stakeholders and end-users [40]. The methodology for developing a TPP for NiV disease should adhere to WHO principles, encompassing a major public health need, considering end-user perspectives, promoting access and equity, and fostering consensus among stakeholders for ethical research and development [41]. Additionally, it should incorporate an end-to-end perspective, connecting product development, regulatory, policy, and financing considerations [40]. This process should involve relevant stakeholders from national and international regulatory agencies, ethics boards, Ministries of Health, and clinicians experienced in treating NiV disease. It is also important to incorporate the needs and preferences of end-users, clinicians, and survivors into the TPP development process to define ideal treatment characteristics.

4.3 Developing rapid point-of-care (PoC) diagnostics:

Rapid diagnostic capability, including PoC testing, is needed for early case detection, and optimal deployment strategies for diagnostics in different geographic areas are required. In-country laboratories must be able to conduct proficiency testing to monitor the reproducibility and

performance of diagnostic assays in the field. National laboratory strategies for NiV diagnosis and detection in the primary affected countries should also be established.

4.4 Clinical trial design:

To progress effectively, we need therapeutic candidates to advance through pre-clinical research, early human safety testing, and manufacturing so that they can be tested clinically, and also clinical trial protocols to ensure a coordinated and standardised assessment of their clinical safety and efficacy.

4.4.1 Pharmacometric trial:

Repurposing existing marketed compounds for treating NiV disease is a potential alternative or complement to developing new drugs, as it capitalizes on their established safety profiles and reduces costs and time, similar to successful approaches used for COVID-19 [42]. Pharmacometric modelling and simulation can be used to model in-vitro activity of potential repurposed therapeutic candidates targeting NiV disease to evaluate the likelihood of clinically significant antiviral activity in vivo[42]. With potential preclinical data in animal models for NiV therapeutic candidates like remdesivir and favipiravir, pharmacometric evaluation of NiV clearance rate from serial oral swabs qPCR viral density estimates may offer a cost-effective and time-efficient method to prioritize potential candidates for further evaluation in clinical trials [43-45].

4.4.2 Core outcome sets, data variables and phase 2/3 trial protocol:

To establish a basis for the development of clinical trial methodology, a core set of data variables and outcome measures should be developed and incorporated into future trial protocols [46]. Consultation and consensus with stakeholders such as clinicians, statisticians, clinical researchers, patient and public health representatives, regulators, and ethics boards are crucial to obtain their views on the trial design. The ultimate goal should be to tools that are freely and publicly available, and ready ahead of time to be implemented in Phase 2/3 therapeutic trials for NiV disease. While containing a recommendation for a core methodology, the tools should allow for context-specific adaptation and use by any member of the NiV research community.

4.4.3 Clinical trial platform and a portfolio approach:

Given the challenges of conducting a phase 3 NiV-specific trial in the current epidemiological conditions, a patient-centred syndromic approach appears more pragmatic. By concentrating on encephalitis, the primary and predominant clinical presentation of NiV disease patients (97% in India, 90% in Bangladesh, 88% in Singapore, 64% in Philippines and 55% in Malaysia), and conducting trials to assess therapeutic approaches for all-cause encephalitis (Figure 1) in endemic regions, we can perhaps significantly improve the management and clinical outcomes of encephalitis at large. Previous encephalitis treatment trials, though limited in number, have not succeeded in improving outcomes. This two-pronged approach, integrating NiV-specific interventions into a broader syndromic strategy, not only addresses encephalitis, a significant health issue, in a patient-centred manner, but also provides a practical solution for dealing with low NiV caseloads and building clinical research capabilities that could respond to a change in epidemiology [23,47,48].

Creating a clinical trial platform, that evaluates therapeutics to treat all-cause encephalitis, complete with a network of strategically-positioned sites that possess enhanced capacity and capability, along with the essential infrastructure required for conducting trials, would be essential to empower local actors to assess clinically candidate treatments they have selected. Given the limited number of available patients and sites where trials can be conducted, the trial should adopt a portfolio approach – where multiple drug candidates can be prioritised and evaluated under a single protocol [4] – using an adaptive design that allows the inclusion of new products as they become available,

either sequentially or simultaneously, and drop those that fail to meet efficacy and safety criteria and not accepted by the community [49].

4.5 Capacity strengthening plan for clinical trials in endemic countries:

To ensure effective clinical trials for NiV disease, it is essential to have adequate research and clinical care and diagnostic capability at participating sites. This would involve mapping out potential study sites and assessing their capacity, including facilities, equipment, human resources, research infrastructure, and background information on NiV disease case management. Capacity gaps should be identified, and capacity strengthening requirements should be defined to assess individual, organizational, and environmental capacity needs, along with the required investments to upgrade. These assessments should be conducted using standardized methods.

Critical investments should be made to boost sustainable research capacity across the NiV research landscape, including training of clinicians and researchers, development of data platforms for observational and multi-county research, outreach and education, and enhanced capacity for data sharing and analysis. Meeting good clinical practice (GCP) and good laboratory practice (GCLP) standards as well as good participatory practice for trials (GPP) will be a prerequisite for participating in these trials.

4.6 Community outreach and engagement:

Understanding the expectations of the NiV-affected community, and involving that community within the research, is essential for successful and impactful research. Furthermore, as NiV research interventions aim to improve the outcomes of those affected by NiV, patients and Nipah survivors should be involved in the decision-making processes which will ultimately affect them and future patients. Examples of this could include community involvement in the TPP development process of new therapeutics, where factors such as acceptable drug administration and side effects can be advised from a community stand-point.

These engagement initiatives will also lead to greater chance of acceptance and implementation of any potential therapeutic interventions. However, social and behavioural barriers may also impact the implementation of interventions through preventing patients from accessing healthcare. NiV-related stigma is one such barrier where tools are currently being developed in collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) to measure the types and extent of stigmatization associated with NiV to reduce this barrier for communities.

Icddr,b, in collaboration with the Institute of Epidemiology Disease Control and Research (IEDCR), the Ministry of Health and Family Welfare, Government of the People's Republic of Bangladesh, has developed a Nipah survivor support program. This program involves following a cohort of Nipah survivors, which includes community members as well as healthcare workers. By involving these survivors in research design and gaining insights into their lived experiences, valuable information can be gathered to inform strategies aimed at helping communities access the healthcare they need whilst also promoting the uptake of potential treatments.

4.7 Developing a viable value proposition and ensuring access to potential therapeutics:

To effectively respond to the urgent public health needs for NiV therapeutics, a comprehensive approach is required that includes securing funding from various sources, advocacy to policy makers and global stakeholders, and the development of a clinical trial platform embedded in the local health system that serves as the central asset around which value is created [3,50]. The value proposition should be informed by a robust assessment of the risk of future outbreaks and the economic, societal, and health impacts that such outbreaks could generate. A partnership between drug developers and the trial sites platform should be defined upfront to serve public health goals,

leveraging different capabilities and financing opportunities towards ultimate availability and access. Having pre-established agreements in place for availability and pricing will avoid repeating the inequalities seen in cases like Ebola and COVID-19 [51].

5 Conclusion:

The recent Ebola, COVID-19, and Mpox epidemics have underscored the importance of a coordinated, public health-centred end-to-end R&D ecosystem that can deliver appropriate countermeasures to address outbreaks where and when they occur [52]. This, both to ensure equitable access to adequate health care for neglected populations, and to prevent onward wider transmission and spillover.

In addressing the challenges posed by NiV, a coordinated public health approach is essential that prioritizes fairness, transparency, and equitable access to interventions for NiV-affected communities. In order to succeed, co-creation and endemic-country leadership and ownership are critical. Collaboration among researchers and institutions within affected nations should empower local communities and ensure they are the primary beneficiaries of research outcomes when needed. To address concerns about equitable access in endemic countries, especially where trials are conducted, post-trial access and benefit-sharing commitments must be integrated into trial protocols, financing contracts, and collaboration agreements, upheld by local authorities and ethics committees. International research institutions and funding bodies must design funding mechanisms with clear conditionalities that prioritize the development of suitable treatment and enable their availability and equitable access.

Contributors

MZH, PH, and PO contributed to the conceptualization of the manuscript. MZH conducted the literature review, led the analysis, wrote, and edited the initial draft. PH and PO provided supervision, feedback, critically reviewed the scientific content, and edited the initial draft. TS, SMS, MZR, JB, AC, and ET critically reviewed, offered feedback, and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

The authors declared no conflicts of interest.

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Table 1: Reported Nipah virus (NiV) cases by country and year, 1998-2023

Country	Year	NiV strain	Primary source of infection	Predominant clinical presentation	Cases	Deaths	Case Fatality Ratio (%)	References
Malaysia	199-1999	NiV-M	Contact with sick pigs	Acute encephalitis	265	105	40	[53]
Singapore	1999	NiV-M	Contact with sick pigs	Acute encephalitis	11	1	9	[16]
India	2001	NiV-B	Unknown	Acute encephalitis	66	45	68	[54]
	2007	NiV-B	Unknown		5	5	100	[55]
	2018	NiV-I	Contact with bats/consumption of bat-contaminated fruit	Acute encephalitis	18	16	89	[35]
	2019	NiV-I	As above	Acute encephalitis	1	0	0	[56]
	2021	NiV-I	As above	Acute encephalitis	1	1	100	[57]
	2023	NiV-I	As above	Acute encephalitis	6	2	33	[21]
Bangladesh	2001	NiV-B	Unknown	Acute encephalitis	13	9	69	[58]
	2003	NiV-B	Unknown	Acute encephalitis	12	8	67	[58]
	2004	NiV-B	Consumption of date palm sap/ fruit contaminated by bat	Acute encephalitis	67	50	75	[58]
	2005	NiV-B	As above	Acute encephalitis	12	11	92	[58]
	2007	NiV-B	As above	Acute encephalitis	18	9	50	[58]
	2008	NiV-B	As above	Acute encephalitis	11	7	64	[58]
	2009	NiV-B	As above	Acute encephalitis	4	1	25	[58]
	2010	NiV-B	As above	Acute encephalitis	18	16	89	[58]
	2011	NiV-B	As above	Acute encephalitis	43	37	86	[58]
	2012	NiV-B	As above	Acute encephalitis	17	12	71	[58]
	2013	NiV-B	As above	Acute encephalitis	31	25	81	[58]
	2014	NiV-B	As above	Acute encephalitis	37	16	43	[58]
	2015	NiV-B	As above	Acute encephalitis	15	11	73	[58]
	2017	NiV-B	As above	Acute encephalitis	3	2	67	[58]
	2018	NiV-B	As above	Acute encephalitis	4	2	50	[58]
	2019	NiV-B	As above	Acute encephalitis	8	7	88	[58]

	2020	NiV-B	As above	Acute encephalitis	7	5	71	[58]
	2021	NiV-B	As above	Acute encephalitis	2	0	0	[58]
	2022	NiV-B	As above	Acute encephalitis	3	2	67	[58]
	2023	NiV-B	As above	Acute encephalitis	14	10	71	[58]
Philippines	2014	NiV-M	Contact with horse/contaminated meat consumption	Acute encephalitis	17	9	53	[59]
	Total	**-**		**-**	**729**	**424**	**58**	**-**

Note: NiV-M: Nipah virus Malaysia, NiV-B: Nipah virus Bangladesh, NiV-I; Nipah virus India

Table 2: Development status of small molecule and monoclonal antibody candidates against Nipah virus [32]

Small molecules	Current regulatory status/development stage	Reference of pre-clinical studies against Nipah virus
Ribavirin	Approved for hepatis C virus and respiratory syncytial virus in several countries	[30]
Remdesivir	Approved for COVID-19 by the US FDA. Emergency use authorisation for COVID-19 in Australia, Bangladesh, India, Singapore, Japan, Taiwan, and the European Union	[43]
Favipiravir	Approved for influenza A in Japan, and for COVID-19 in several countries. Emergency use authorisation for COVID-19 in India	[44]
Chloroquine	Approved for malaria in several countries	[60]
Heparin	Approved for coagulopathies in several countries. Experimental: preclinical (Syrian golden hamster study)	[61]
Rintatolimid	Approved for chronic fatigue syndrome in Argentina. Experimental (phase 1 and 2 trials) for HIV and chronic fatigue syndrome	[62]
Griffithsin	Experimental: phase 1 trials for HIV	[63]
VIKI-dPEG4- Toco, VIKI-PEG4- chol	Experimental: preclinical	[64]
Gliotoxin	Experimental: exploratory	[65]
Bortezomib	Approved for multiple myeloma and mantle cell lymphoma by the US FDA	[66]
Balapiravir, R1479	Experimental, discontinued in phase 1 trials for dengue virus and hepatitis C virus	[67]
Lumicitabine, ALS-8112	Experimental: phase 1 and phase 2 trials for respiratory syncytial virus	[68]
CH25H	Experimental: exploratory	[69]
KIN1408	Experimental: exploratory	[70]
AB00991123, AB00992391, and AB00993210	Experimental: exploratory	[71]
Monoclonal antibodies (mAb)		
mAb 102·4	Phase 1	[29]
mAb 5B3, mAb h5B3·1	Preclinical	[72,73]
mAb HENV-26, mAb HENV-32	Preclinical	[74]
Anti-G mAb (Nip GIP 1.7 and Nip 3B10) , anti-F mAb (Nip GIP 35 and Nip GIP 3)	Preclinical	[75]

Note: Adapted from Román RG, Tornieporth N, Cherian NG, et al. Medical countermeasures against henipaviruses: A review and public health perspective. The Lancet Infectious Diseases 2022; 22(1): e13-e27. Copyright © 2022 Elsevier Ltd.

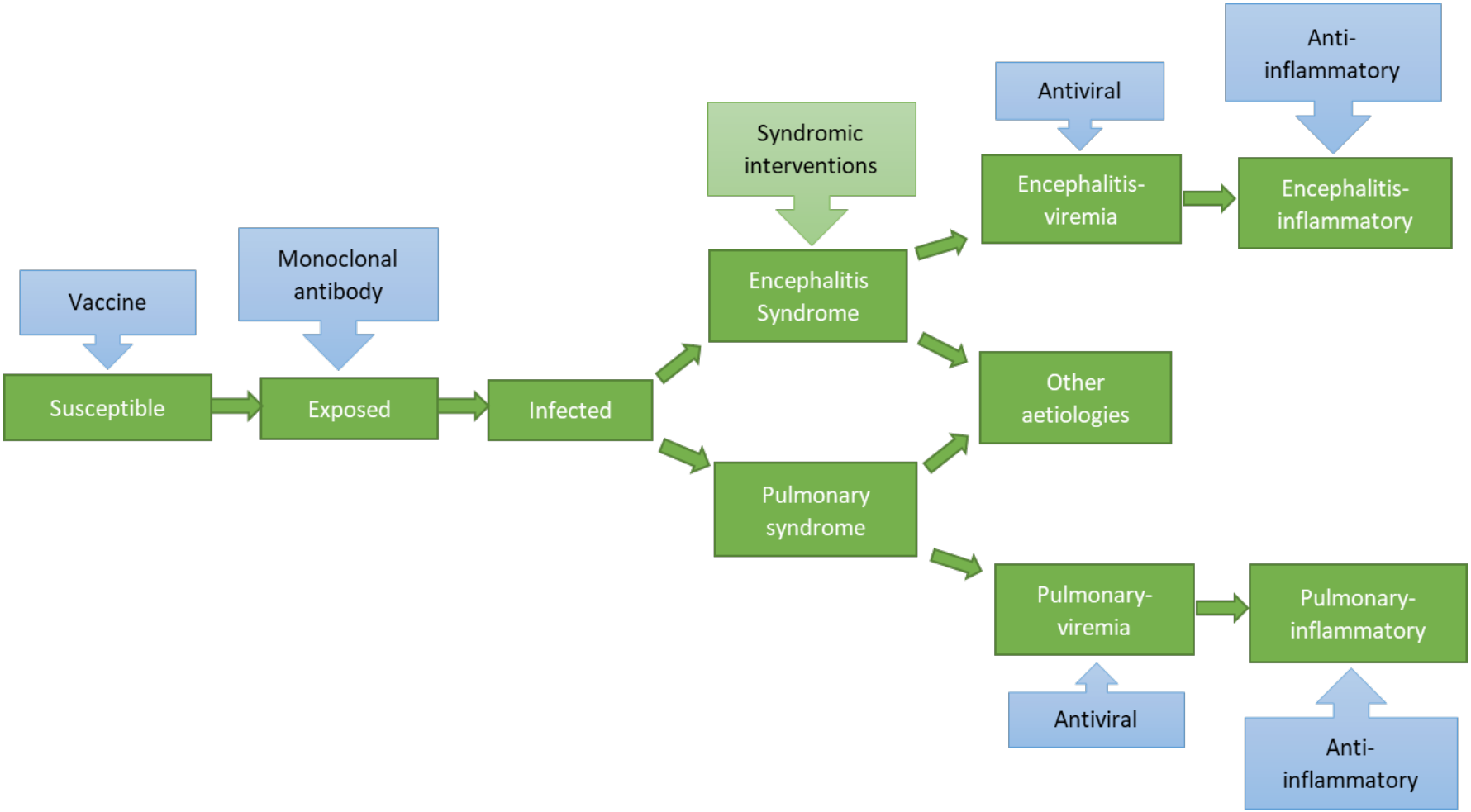

Figure 1: Schematic diagram depicting potential interventions for Nipah virus disease

References:

1. WHO. WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern. 2022. https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern#:~:text=On%20July%2023%2C%20the%20WHO,in%20the%20WHO%20European%2 (accessed July 26 2023).
2. Nakoune E, Olliaro P. Waking up to monkeypox. *BMJ* 2022; **377**: o1321.
3. Torreele E, Boum Y, Adjaho I, et al. Breakthrough treatments for Ebola virus disease, but no access—what went wrong, and how can we do better? *The Lancet Infectious Diseases* 2023.
4. Olliaro P, Torreele E. Global challenges in preparedness and response to epidemic infectious diseases. *Molecular Therapy* 2022; **4**(30): 1801-9.
5. Parashar UD, Sunn LM, Ong F, et al. Case-control study of risk factors for human infection with a new zoonotic paramyxovirus, Nipah virus, during a 1998–1999 outbreak of severe encephalitis in Malaysia. *The Journal of infectious diseases* 2000; **181**(5): 1755-9.
6. Nikolay B, Salje H, Hossain MJ, et al. Transmission of Nipah virus—14 years of investigations in Bangladesh. *New England Journal of Medicine* 2019; **380**(19): 1804-14.
7. Luby SP. The pandemic potential of Nipah virus. *Antiviral research* 2013; **100**(1): 38-43.
8. Gurley ES, Montgomery JM, Hossain MJ, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. *Emerging infectious diseases* 2007; **13**(7): 1031.
9. Nowak RM, Walker EP. Walker's Mammals of the World: JHU press; 1999.
10. Rahman MZ, Islam M, Hossain M, et al. Genetic diversity of Nipah virus in Bangladesh. *International Journal of Infectious Diseases* 2021; **102**: 144-51.
11. WHO. Prioritizing diseases for research and development in emergency contexts. 2018. https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts (accessed 19 April 2023).
12. WHO. Nipah Research and Development (R&D) Roadmap. 2019. https://www.who.int/publications/m/item/nipah-research-and-development-(r-d)-roadmap (accessed July 15 2023).
13. CEPI.Our portfolio-Nipah virus. 2023. https://cepi.net/research_dev/our-portfolio/ (accessed April 19 2023).
14. Goh KJ, Tan CT, Chew NK, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *New England Journal of Medicine* 2000; **342**(17): 1229-35.
15. Hossain MJ, Gurley ES, Montgomery JM, et al. Clinical presentation of nipah virus infection in Bangladesh. *Clinical infectious diseases* 2008; **46**(7): 977-84.
16. Paton NI, Leo YS, Zaki SR, et al. Outbreak of Nipah-virus infection among abattoir workers in Singapore. *The Lancet* 1999; **354**(9186): 1253-6.
17. Kenmoe S, Demanou M, Bigna JJ, et al. Case fatality rate and risk factors for Nipah virus encephalitis: A systematic review and meta-analysis. *Journal of Clinical Virology* 2019; **117**: 19-26.
18. Harcourt BH, Tamin A, Ksiazek TG, et al. Molecular characterization of Nipah virus, a newly emergent paramyxovirus. *Virology* 2000; **271**(2): 334-49.
19. Luby SP, Rahman M, Hossain MJ, et al. Foodborne transmission of Nipah virus, Bangladesh. *Emerging infectious diseases* 2006; **12**(12): 1888.
20. IEDCR. NIPAH Virus Update. https://www.iedcr.gov.bd/site/notices/28d003a9-65a2-49b4-ac2d-503b489a57f3/NIPAH-Virus-Update-04-March-2023 (accessed 19th April 2023).
21. ProMED. 2023. https://promedmail.org/promed-posts/ (accessed September 23 2023).
22. Mazzola LT, Kelly-Cirino C. Diagnostics for Nipah virus: a zoonotic pathogen endemic to Southeast Asia. *BMJ global health* 2019; **4**(Suppl 2): e001118.

23. Paul KK, Sazzad HM, Rahman M, et al. Hospital-based surveillance for Japanese encephalitis in Bangladesh, 2007–2016: Implications for introduction of immunization. *International Journal of Infectious Diseases* 2020; **99**: 69-74.
24. Sazzad HM, Hossain MJ, Gurley ES, et al. Nipah virus infection outbreak with nosocomial and corpse-to-human transmission, Bangladesh. *Emerging infectious diseases* 2013; **19**(2): 210.
25. Hassan MZ, Sazzad HM, Luby SP, et al. Nipah virus contamination of hospital surfaces during outbreaks, Bangladesh, 2013–2014. *Emerging infectious diseases* 2018; **24**(1): 15.
26. IEDCR. National Guideline for Mangment, Prevention and Control of Nipah Virus Infection including Encephalities 2023. https://www.moh.gov.bt/wp-content/uploads/afd-files/2014/11/WHO-guideline-for-Management-Prevention-and-Control-of-Nipah-Virus-Infection.pdf (accessed May 11 2023).
27. Gurley ES, Spiropoulou CF, De Wit E. Twenty years of Nipah virus research: where do we go from here? *The Journal of infectious diseases* 2020; **221**(Supplement_4): S359-S62.
28. Nikolay B, Salje H, Khan AD, et al. A framework to monitor changes in transmission and epidemiology of emerging pathogens: lessons from Nipah virus. *The Journal of Infectious Diseases* 2020; **221**(Supplement_4): S363-S9.
29. Playford EG, Munro T, Mahler SM, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of a human monoclonal antibody targeting the G glycoprotein of henipaviruses in healthy adults: a first-in-human, randomised, controlled, phase 1 study. *The Lancet Infectious Diseases* 2020; **20**(4): 445-54.
30. Chong HT, Kamarulzaman A, Tan CT, et al. Treatment of acute Nipah encephalitis with ribavirin. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 2001; **49**(6): 810-3.
31. Hoogstraaten MJ, Boon WP, Frenken K. How product development partnerships support hybrid collaborations dealing with global health challenges. *Global Transitions* 2020; **2**: 190-201.
32. Román RG, Tornieporth N, Cherian NG, et al. Medical countermeasures against henipaviruses: A review and public health perspective. *The Lancet Infectious Diseases* 2022; **22**(1): e13-e27.
33. ISARIC. West Africa Lassa fever Consortium (WALC). https://isaric.org/research/lassa-fever-resources/walc/ (accessed April 19 2023).
34. WHO. Good Participatory Practice for trials of (re-)emerging pathogens (GPP-EP): Guidelines. 2023. https://www.who.int/publications/m/item/good-participatory-practice-guidelines-for-trials-of-emerging-(and-re-emerging)-pathogens-that-are-likely-to-cause-severe-outbreaks-in-the-near-future-and-for-which-few-or-no-medical-countermeasures-exist-(gpp-ep)#:~:text=GPP%2DEP%20is%20the%20only,quality%20and%20outcomes%20of%20research (accessed 22 September 2023).
35. Chandni R, Renjith T, Fazal A, et al. Clinical manifestations of nipah virus–infected patients who presented to the emergency department during an outbreak in Kerala State in India, May 2018. *Clinical Infectious Diseases* 2020; **71**(1): 152-7.
36. Escaffre O, Borisevich V, Vergara LA, Wen JW, Long D, Rockx B. Characterization of Nipah virus infection in a model of human airway epithelial cells cultured at an air–liquid interface. *The Journal of general virology* 2016; **97**(Pt 5): 1077.
37. Mire CE, Satterfield BA, Geisbert JB, et al. Pathogenic differences between Nipah virus Bangladesh and Malaysia strains in primates: implications for antibody therapy. *Scientific reports* 2016; **6**(1): 30916.
38. Rockx B, Bossart KN, Feldmann F, et al. A novel model of lethal Hendra virus infection in African green monkeys and the effectiveness of ribavirin treatment. *Journal of virology* 2010; **84**(19): 9831-9.
39. Paton, N I, Leo, et al. Outbreak of Nipah-virus infection among abattoir workers in Singapore. *Lancet* 1999; **354**(9186): 1253-6.

40. WHO. Target product profiles. 2023. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles (accessed April 19 2023).
41. Charnaud SC, Moorthy V, Reeder J, Ross AL. WHO target product profiles to shape global research and development. *Bulletin of the World Health Organization* 2023; **101**(5): 326.
42. Wattanakul T, Chotsiri P, Scandale I, Hoglund RM, Tarning J. A pharmacometric approach to evaluate drugs for potential repurposing as COVID-19 therapeutics. *Expert Review of Clinical Pharmacology* 2022; **15**(8): 945-58.
43. Lo MK, Feldmann F, Gary JM, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Science translational medicine* 2019; **11**(494): eaau9242.
44. Dawes BE, Kalveram B, Ikegami T, et al. Favipiravir (T-705) protects against Nipah virus infection in the hamster model. *Scientific reports* 2018; **8**(1): 7604.
45. Schilling WH, Jittamala P, Watson JA, et al. Pharmacometrics of high dose ivermectin in early COVID-19: an open label, randomized, controlled adaptive platform trial (PLATCOV). *Elife* 2023; **12**.
46. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; **13**(1): 1-8.
47. Narain JP, Dhariwal A, MacIntyre CR. Acute encephalitis in India: An unfolding tragedy. *The Indian journal of medical research* 2017; **145**(5): 584.
48. Jain P, Jain A, Kumar A, et al. Epidemiology and etiology of acute encephalitis syndrome in North India. *Japanese journal of infectious diseases* 2014; **67**(3): 197-203.
49. Pessoa-Amorim G, Campbell M, Fletcher L, et al. Making trials part of good clinical care: lessons from the RECOVERY trial. *Future Healthcare Journal* 2021; **8**(2): e243.
50. ISARIC. Developing a value proposition for sustainable R&D and availability of Lassa fever therapeutics in West Africa. 2023. https://isaricdev.wpenginepowered.com/wp-content/uploads/2023/03/WALC_Value-Proposition.pdf (accessed 22 September 2023).
51. Torreele E, Wolfe D, Kazatchkine M, et al. From private incentives to public health need: rethinking research and development for pandemic preparedness. *The Lancet Global Health* 2023.
52. Torreele E, Kazatchkine M, Liu J, et al. Stopping epidemics when and where they occur. *The Lancet* 2023; **401**(10374): 324-8.
53. Lam SK, Chua KB. Nipah virus encephalitis outbreak in Malaysia. *Clinical Infectious Diseases* 2002; **34**(Supplement_2): S48-S51.
54. Chadha MS, Comer JA, Lowe L, et al. Nipah virus-associated encephalitis outbreak, Siliguri, India. *Emerging infectious diseases* 2006; **12**(2): 235.
55. Arankalle VA, Bandyopadhyay BT, Ramdasi AY, et al. Genomic characterization of nipah virus, west bengal, India. *Emerging infectious diseases* 2011; **17**(5): 907.
56. Sahay RR, Yadav PD, Gupta N, et al. Experiential learnings from the Nipah virus outbreaks in Kerala towards containment of infectious public health emergencies in India. *Epidemiology & Infection* 2020; **148**.
57. Yadav PD, Sahay RR, Balakrishnan A, et al. Nipah virus outbreak in Kerala State, India amidst of COVID-19 pandemic. *Frontiers in Public Health* 2022; **10**: 14.
58. IEDCR. Nipah case update in 2023. https://www.iedcr.gov.bd/site/notices/28d003a9-65a2-49b4-ac2d-503b489a57f3/NIPAH-Virus-Update-04-March-2023 (accessed April 19 2023).
59. Ching PKG, de Los Reyes VC, Sucaldito MN, et al. Outbreak of henipavirus infection, Philippines, 2014. *Emerging infectious diseases* 2015; **21**(2): 328.
60. Pallister J, Middleton D, Crameri G, et al. Chloroquine administration does not prevent Nipah virus infection and disease in ferrets. *Journal of virology* 2009; **83**(22): 11979-82.
61. Mathieu C, Dhondt KP, Châlons M, et al. Heparan sulfate-dependent enhancement of henipavirus infection. *MBio* 2015; **6**(2): 10.1128/mbio. 02427-14.

62. Georges-Courbot M, Contamin H, Faure C, et al. Poly (I)-poly (C12U) but not ribavirin prevents death in a hamster model of Nipah virus infection. *Antimicrobial agents and chemotherapy* 2006; **50**(5): 1768-72.
63. Lo MK, Spengler JR, Krumpe LR, et al. Griffithsin inhibits Nipah virus entry and fusion and can protect Syrian golden hamsters from lethal Nipah virus challenge. *The Journal of infectious diseases* 2020; **221**(Supplement_4): S480-S92.
64. Mathieu C, Porotto M, Figueira TN, Horvat B, Moscona A. Fusion inhibitory lipopeptides engineered for prophylaxis of Nipah virus in primates. *The Journal of Infectious Diseases* 2018; **218**(2): 218-27.
65. Aljofan M, Sganga ML, Lo MK, et al. Antiviral activity of gliotoxin, gentian violet and brilliant green against Nipah and Hendra virus in vitro. *Virology Journal* 2009; **6**(1): 1-13.
66. Wang YE, Park A, Lake M, et al. Ubiquitin-regulated nuclear-cytoplasmic trafficking of the Nipah virus matrix protein is important for viral budding. *PLoS pathogens* 2010; **6**(11): e1001186.
67. Hotard AL, He B, Nichol ST, Spiropoulou CF, Lo MK. 4′-Azidocytidine (R1479) inhibits henipaviruses and other paramyxoviruses with high potency. *Antiviral research* 2017; **144**: 147-52.
68. Lo MK, Amblard F, Flint M, et al. Potent in vitro activity of β-D-4′-chloromethyl-2′-deoxy-2′-fluorocytidine against Nipah virus. *Antiviral research* 2020; **175**: 104712.
69. Liu S-Y, Aliyari R, Chikere K, et al. Interferon-inducible cholesterol-25-hydroxylase broadly inhibits viral entry by production of 25-hydroxycholesterol. *Immunity* 2013; **38**(1): 92-105.
70. Pattabhi S, Wilkins CR, Dong R, et al. Targeting innate immunity for antiviral therapy through small molecule agonists of the RLR pathway. *Journal of virology* 2016; **90**(5): 2372-87.
71. Tigabu B, Rasmussen L, White EL, et al. A BSL-4 high-throughput screen identifies sulfonamide inhibitors of Nipah virus. *Assay and drug development technologies* 2014; **12**(3): 155-61.
72. Dang HV, Chan Y-P, Park Y-J, et al. An antibody against the F glycoprotein inhibits Nipah and Hendra virus infections. *Nature structural & molecular biology* 2019; **26**(10): 980-7.
73. Mire CE, Chan Y-P, Borisevich V, et al. A cross-reactive humanized monoclonal antibody targeting fusion glycoprotein function protects ferrets against lethal Nipah virus and Hendra virus infection. *The Journal of infectious diseases* 2020; **221**(Supplement_4): S471-S9.
74. Dong J, Cross RW, Doyle MP, et al. Potent henipavirus neutralization by antibodies recognizing diverse sites on Hendra and Nipah virus receptor binding protein. *Cell* 2020; **183**(6): 1536-50. e17.
75. Guillaume V, Contamin H, Loth P, et al. Antibody prophylaxis and therapy against Nipah virus infection in hamsters. *Journal of virology* 2006; **80**(4): 1972-8.