Interpreting the natural history and pathogenesis of Nipah virus disease through clinical data, to inform clinical trial design: a systematic review

Md Zakiul Hassan, Susan Khader Ibrahim, Eli Harriss, Peter Horby, Piero Olliaro, Amanda Rojek

Nipah virus is a priority pathogen with high mortality and pandemic potential. Therapies for Nipah virus disease, such as monoclonal antibodies and antivirals, are under development and require clinical trials for evaluation. However, designing such trials is challenging due to the limited understanding of the clinical characteristics, pathogenesis, and current management of Nipah virus disease. In this Review, we gathered essential data from 59 studies reporting 717 Nipah virus disease cases, to inform trial design. Nearly all patients (618 [99%] of 624) had fever. Neurological symptoms included headache (419 [70%] of 601 patients), confusion (74 [65%] of 114), and altered consciousness (358 [62%] of 580); respiratory symptoms included cough (244 [45%] of 541) and difficulty in breathing (184 [58%] of 317). Imaging data revealed chest abnormalities (29 [80%] of 36) and brain involvement (40 [71%] of 56). Viral RNA was detectable early in illness across various sample types. The median case-fatality rate was 69% (IQR 31–88%), with 51 (26%) of 197 survivors presenting with persistent neurological deficits. Clinical management varied widely, with incomplete reporting limiting insights. Prospective observational studies are needed to generate actionable data on clinical case definitions, predictors of adverse outcomes, current standards of care, and standardised endpoints, to inform future trials.

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See Online for appendix

Introduction

Nipah virus is a recognised threat to global health security.[1] First identified in 1998, following an outbreak among pig farmers in Malaysia and Singapore, Nipah virus has since caused recurrent outbreaks, particularly in Bangladesh and India.[2,3] Although human infections are currently confined to south and southeast Asia, WHO classifies Nipah virus as a priority pathogen due to its extensive reservoir host range, potential for human-to-human transmission, and the absence of approved vaccines or treatments for the condition, raising concerns about future outbreaks.[4]

Nipah virus primarily affects the CNS and respiratory system, causing acute encephalitis and acute respiratory distress with high mortality.[2] No systematic approach exists as yet to improve patient care, and the current management is limited to supportive care. Advancing clinical care for patients with Nipah virus disease (NiVD) is crucial to improve patient outcomes during ongoing outbreaks and to prepare for potential epidemics.

Potential therapeutic candidates for NiVD that are currently progressing through the research and development pipeline include monoclonal antibodies and small molecule antivirals.[5] Current animal model data support potential in-human trial for m102.4, Hu1F5, and remdesivir, either alone or in combination.[5] Phase 1 safety data for m102.4 are available from an Australian trial; however, further development of m102.4 has not progressed, because the more potent Hu1F5 has shown superior efficacy in non-human primate models and is now advancing to phase 1 evaluation in the USA.[6] These potential new and repurposed treatments will need to be evaluated for safety and efficacy in clinical trials.

However, designing trials for potential therapeutics is challenging due to the limited understanding of NiVD's clinical characteristics, pathogenesis, and current management. In this systematic review, we gathered essential data to inform clinical trial design, including the frequency of key patient outcomes (necessary for defining primary outcomes of the trial and estimating sample size), timing of outcomes (crucial for identifying when to measure each outcome), predictors of adverse outcomes (needed for stratifying randomisation or adjusting analyses), and the current standard of care (to be used as a comparator).[7]

Methods

Registration

This systematic review was registered prospectively on the PROSPERO database (CRD42023463537)[8] and adheres to the PRISMA 2020 reporting guidelines[9] (appendix pp 3–5).

Search strategy and selection criteria

The electronic bibliographic databases PubMed, Ovid Embase, Ovid CAB Abstracts, Ovid Global Health, Scopus, Web of Science Core Collection, and WHO Global Index Medicus were searched without language and publication date restrictions. All searches were conducted on June 22, 2023, and then updated on Aug 20, 2025. The search strategy and methodology are outlined in the appendix (pp 5–6). Studies reporting primary data on clinical and pathological features of acute Nipah virus infections in humans and human tissues were included. Animal studies, in-silico studies, and in-vitro studies were excluded.

Data extraction and synthesis

Two independent reviewers (MZH and SKI) screened titles, abstracts, and full texts to agree on study eligibility and extracted the following information from each study: study

setting, study design, laboratory tests used, proportion of confirmed cases, clinical and pathological features, and clinical outcomes. The proportion of patients presenting specific clinical and pathological features was recorded. A narrative synthesis was conducted when quantitative synthesis was not possible due to the heterogeneity of data.

Data analysis

The prevalence of signs and symptoms was calculated by dividing the number of patients presenting each sign or symptom by the total number of patients assessed for the same, as reported in the publication. To count the total number of NiVD cases, the largest cohort per outbreak was used, and for multioutbreak reports, the publication covering the most outbreaks and cases was prioritised, to avoid duplication. Similarly, when analysing clinical signs and symptoms, a stepwise prioritisation process was applied, selecting studies with the largest number of laboratory-confirmed cases, followed by the overall sample size, and then the breadth of clinical information. Case-fatality rate (CFR) was reported on the basis of the number of deaths among the laboratory-confirmed cases.

For time-related data, the minimum and maximum durations (in days) for key clinical intervals were extracted, including time from symptom onset to presentation, symptom onset to hospital admission, incubation period, and hospital admission to outcome. These intervals were reported, along with their mean, median, IQR, and range.

To compare clinical features and outcomes between patients infected with the Nipah virus-Malaysia (NiV-M) and Nipah virus-Bangladesh (NiV-B) strains, χ^2 test or Fisher's exact test was used, as appropriate. A p-value of less than 0·05 was considered statistically significant. R version 4.3.1 was used to perform all statistical analyses and prepare figures.

Quality assessment

We used the Joanna Briggs Institute (JBI) critical appraisal tools to assess the risk of bias in the included studies.[10,11] Each study was evaluated on the basis of the specific criteria outlined in the JBI Manual for Evidence Synthesis.[10]

Review team and tools

At least two independent reviewers (MZH and SKI) performed screening (titles and abstracts, followed by full texts), agreed upon study eligibility, extracted data, and undertook risk-of-bias assessment using DistillerSR version 2.35.

For more on **DistillerSR**, see https://www.distillersr.com/

Results

Study characteristics

We identified 59 eligible publications[3,12–63] (figure 1). Over half (38 [64%] of 59) of the publications were case reports or case series. The studies were reported from five countries: Bangladesh (22), India (19), Malaysia (11), Singapore (six), and the Philippines (one; appendix p 7).

The number of publications reporting each outbreak ranged between one and 11 and cumulatively included 2239 participants (appendix pp 8–9). In total, the included publications reported 717 discrete patients with NiVD from the five countries. Bangladesh (325 [45%] of 717) and Malaysia (265 [37%]) accounted for the most cases.

Case confirmation and diagnostics methods

Nearly all publications (56 [95%] of 59) reported confirming the cases using Nipah virus-specific laboratory tests, either alone or in conjunction with clinical and epidemiological criteria. A clinical case definition was mentioned in 25 (44%) of the 56 publications. The most used clinical criteria were presence of fever plus neurological features (altered mental status, seizure, or neurological deficit; 12 [48%] of 25; figure 2). Two publications (4%) of 56 reported exclusion criteria: fever of known cause and age less than 2 years.

The predominant method of laboratory confirmation was serology, detecting Nipah virus IgM in serum (27 [53%] of 51), followed by serology combined with real-time (rt)RT-PCR (14 [27%] of 51) and rtRT-PCR alone (ten [20%] of 51).

Characteristics of the NiVD cases

Data on age were available for 412 patients, with an age range of 2 years to 100 years. Most (244 [59%] of 417) of the patients were aged 30 years or younger. Data on sex were available for 642 patients, with 438 (68%) of 647 of them being men (appendix p 13). Only one description of a pregnant woman was identified.[42]

Presenting symptoms

At baseline, nearly all patients (618 [99%] of 624) among those assessed had fever (figure 3). Patients primarily presented with neurological or respiratory symptoms, or both. Headache (419 [70%] of 601), confusion (74 [65%] of 114), and altered consciousness (358 [62%] of 580) were the predominant neurological symptoms, whereas difficulty breathing (184 [58%] of 317) and cough (244 [45%] of 541) were frequent respiratory symptoms. Gastrointestinal symptoms, such as excessive salivation (44 [95%] of 46) and anorexia (45 [36%] of 125), were also common; however, these two symptoms were assessed and reported in only a few (one to three) studies.

The trend of common clinical signs and symptoms, particularly respiratory symptoms, differed between the two Nipah virus strains (NiV-M and NiV-B). Cough (17 [16%] of 105 for NiV-M *vs* 169 [49%] of 343 for NiV-B; p<0·0001) and shortness of breath (two [2%] of 103 for NiV-M *vs* 213 [51%] of 411 for NiV-B; p<0·0001) were significantly more common among patients infected with NiV-B than in those infected with NiV-M. Fatigue, malaise, or lethargy (21 [20%] of 104 for NiV-M *vs* 283 [70%] of 402 for NiV-B; p<0·0001); vomiting (41 [36%] of 114 for NiV-M *vs* 254 [51%] of 496 for NiV-B; p=0·0036); anorexia (28 [27%] of 103 for NiV-M *vs* 17 [77%] of 22 for NiV-B;

p<0·0001); joint pain (seven [7%] of 103 for NiV-M *vs* 71 [23%] of 308 for NiV-B; p<0·0001); and altered consciousness (23 [23%] of 101 for NiV-M *vs* 335 [70%] of 479 for NiV-B; p<0·0001) were also more frequent in patients infected with NiV-B than in those infected with NiV-M. In contrast, some systemic and neurological features, notably chills (53 [51%] of 103 for NiV-M *vs* five [23%] of 22 for NiV-B; p=0·018), headache (99 [87%] of 114 for NiV-M *vs* 320 [66%] of 487 for NiV-B; p<0·0001), disorientation (24 [75%] of 32 for NiV-M *vs* six [27%] of 22 for NiV-B; p<0·0001), and myoclonus (56 [51%] of 110 for NiV-M *vs* eight [16%] of 49 for NiV-B; p<0·0001) were more common in patients infected with NiV-M than in those infected with NiV-B (appendix pp 14–16).

Laboratory and imaging features

Heterogeneity existed in the way laboratory results were presented; some publications only reported the number of cases with abnormal laboratory results without indicating actual values or a summary of findings, whereas others reported a summary finding of the reported laboratory values, without indicating a cutoff. In this Review, the findings were categorised according to the standard cutoff for each parameter (appendix pp 17–20).

Elevated white blood cell counts (>5 cells per mm^3) with a predominance of lymphocytes, elevated red blood cell counts (>1 cell per mm^3), high protein concentrations (>0·4 g/L), and high glucose concentrations (>4·2 mmol/L) as compared with the common reference ranges were generally observed. Further detail of cerebrospinal fluid findings, haematological findings, and liver and renal function tests are included in the appendix (pp 17–20).

Chest radiographs revealed abnormalities in 29 (80%) of 36 patients with NiVD who underwent imaging, with findings suggestive of bilateral pulmonary infiltrates consistent with viral pneumonitis or acute respiratory distress syndrome (appendix pp 20–21).

Nine publications reported brain MRI findings for 56 NiVD cases. Overall, MRI findings frequently showed hyperintense lesions, with 40 (71%) of 56 of the imaged patients displaying abnormalities (appendix pp 20–21).

Presence of Nipah virus RNA in body fluids

Detection of Nipah virus RNA across various body fluids was reported for 36 patients: oral or throat swabs (26), urine (nine), serum (11), cerebrospinal fluid (six), endotracheal aspirate (one), semen (one), and breastmilk (one). Several patients (14) had multiple samples tested (figure 4). Overall detection rates among the tested samples, irrespective of the number of patients, were one (100%) of one for endotracheal aspirates and breastmilk, five (83%) of six for cerebrospinal fluid, 38 (70%) of 54 for oral or throat swabs, 13 (52%) of 25 for urine, two (50%) of four for semen, and ten (32%) of 31 for blood.

Nipah virus RNA was detectable in throat swabs as early as day 1 after onset of illness and remained detectable up to day 14. Nipah virus RNA became undetectable between days 14 and 20 in patients who survived. Viral RNA was most frequently detected in the serum between days 4 to 10 after onset of illness, with a clear decrease in detection beyond day 10. Patients who survived often showed a transition from viraemia (presence of viral RNA in the blood) to undetectable Nipah virus RNA over time, particularly after the first 10 days.

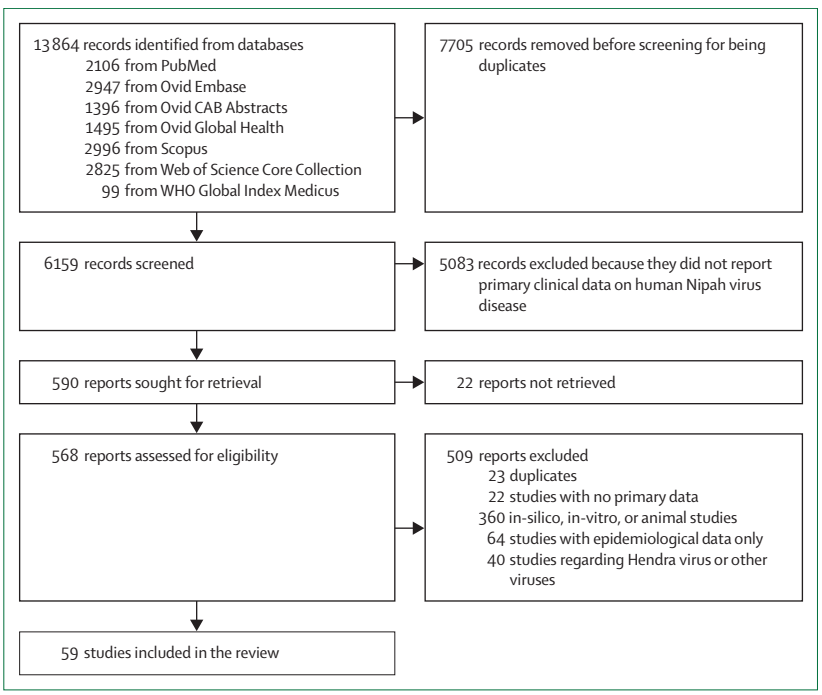

Figure 1: **PRISMA flow diagram**

Detection of Nipah virus RNA in cerebrospinal fluid was reported for five patients. The earliest Nipah virus RNA detection among those days' samples were collected and tested from day 5 to day 7 after symptom onset, with the latest detection occurring on day 12 (appendix p 21).

For patients who had multiple body fluids tested, Nipah virus RNA was typically detectable first in oral or throat swabs as early as day 2, in blood between days 5 and 9, and in cerebrospinal fluid between days 5 and 12, depending on the sample timing and fluid type. These data show that Nipah virus RNA detection varies across body fluids and over time, with viral presence peaking during the first 10 days of illness and gradually becoming undetectable.

Risk factors of severe disease

Five publications reported demographic, clinical, or laboratory findings associated with prognosis. In three publications, two from Malaysia (NiV-M) and one from Bangladesh (NiV-B), multivariable analysis was conducted, whereas two studies, one from each country, showed associations in univariate analysis (appendix p 23). Factors

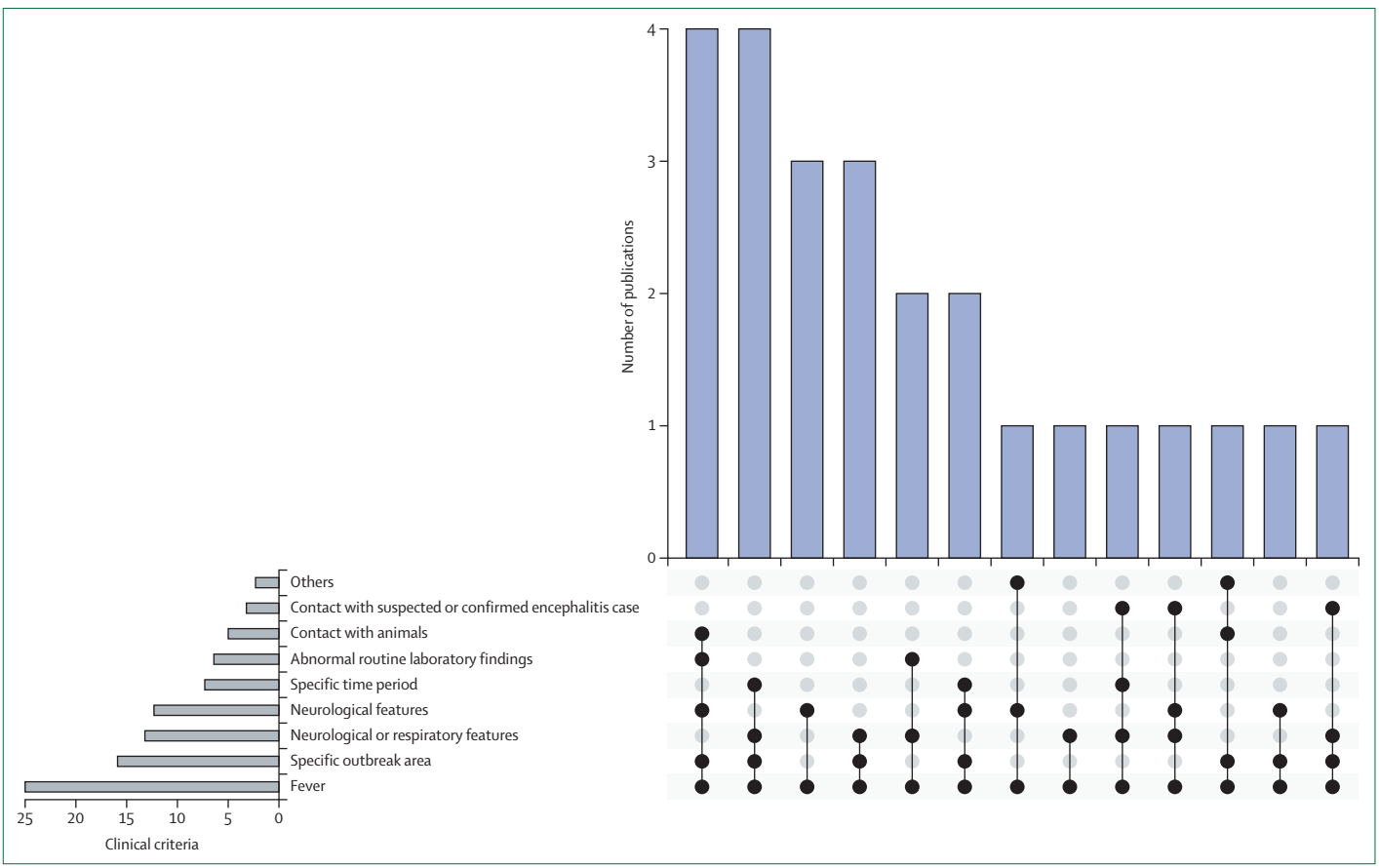

Figure 2: **Frequency of publications using common combinations of clinical and epidemiological criteria in case definitions**
Neurological features include new-onset altered mental status or sensorium, new-onset seizures, or new neurological deficits, which could be diffused or localised and focal to the brain. Respiratory symptoms include cough, shortness of breath, and difficulty breathing. Abnormal laboratory findings include atypical results from cerebrospinal fluid analysis or MRI. Specified time period means symptom onset within outbreak-defined dates. Specified outbreak area means residence in or travel to the affected locality during that period. Other criteria include hospitalisation in a specific facility and age of more than 15 years.

such as altered mental status, unconsciousness, myoclonus, tachycardia, high fever (>37·8°C), and hypertension were associated with mortality in the multivariable analysis conducted in at least two studies. Increasing age, presence of convulsions, absent or reduced reflexes, and extensor plantar responses were associated with poor prognosis among patients infected with NiV-M but not among those infected with NiV-B. Among serologically confirmed patients (presence of IgM in serum), patients who died were more likely to have detectable Nipah virus RNA in oral swabs and cerebrospinal fluid detected during hospital stay, as compared with those who survived.

Temporal dynamics of NiVD progression

NiVD shows a variable incubation period—the time between exposure to symptom onset—with the median reported per outbreak ranging from 3·2 to 10 days (appendix pp 23–24). The overall median duration from onset of symptoms to hospital admission was between 3 to 4 days. Intensive care unit admission was noted at a median of 6 days in Malaysia. The duration of hospitalisation varied substantially between countries, with deaths occurring within 2 to 4 days of hospital admission and discharges ranging from 8 to 19 days. The overall duration of illness extended up to 22 days.

Pathological features of NiVD cases

The characteristic pathological changes observed included vasculitis of small-sized and medium-sized vessels in one or more organs, thrombosis, and microinfarcts in the CNS, along with fibrinoid necrosis in the pulmonary alveoli and renal glomeruli (appendix p 24).

Clinical management of NiVD cases

22 publications included data on the clinical management of patients with NiVD, covering the use of antivirals (20), antibiotics (eight), and corticosteroids (three), with several publications contributing to more than one treatment category. The antivirals most often used were ribavirin, aciclovir, oseltamivir, and remdesivir (appendix p 24). Broad-spectrum antibiotics, including ceftriaxone and

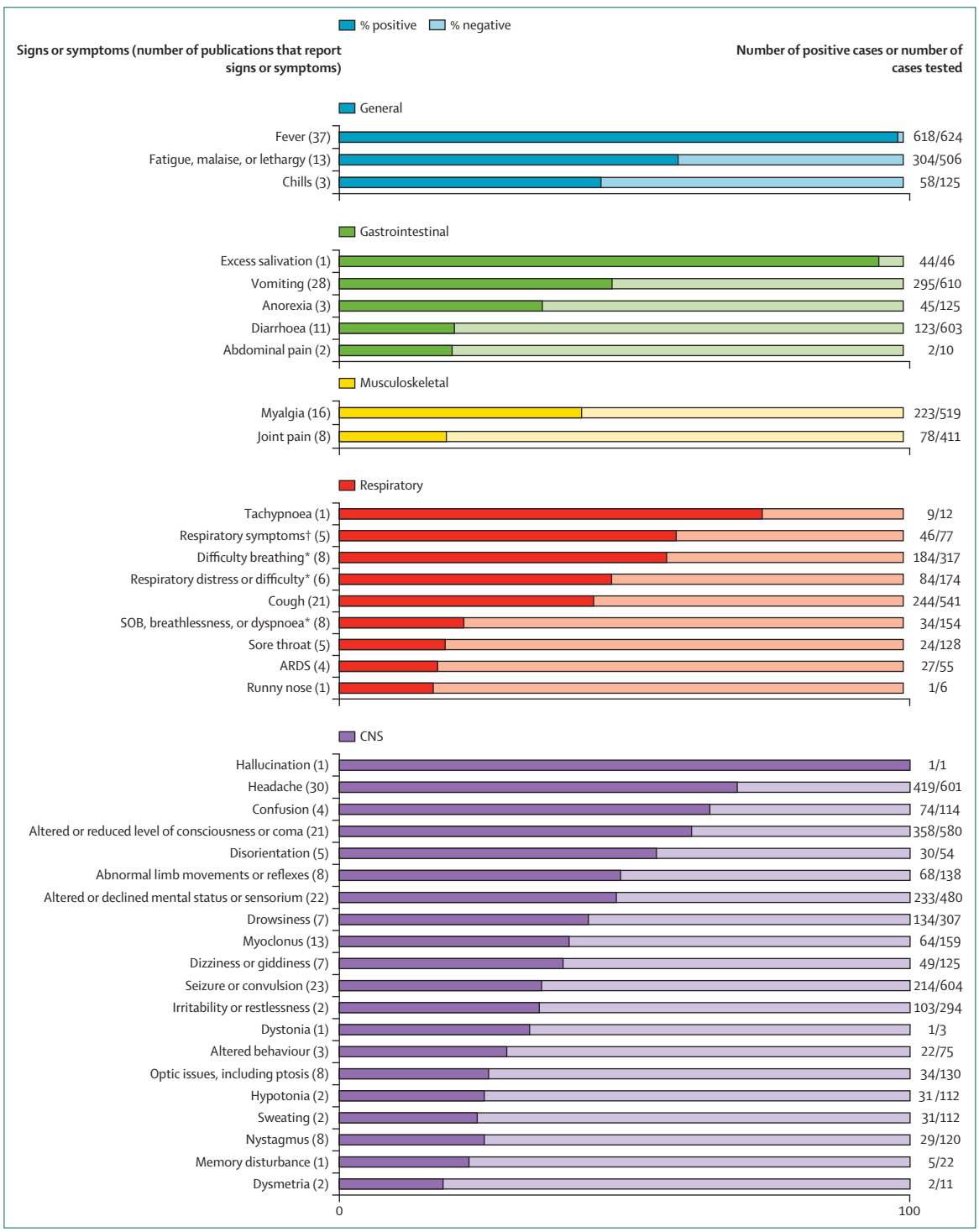

Figure 3: **Clinical presentation of Nipah virus disease cases**

*Excludes the mention of ARDS. †All other descriptions of respiratory syndromes. ARDS=acute respiratory distress syndrome. SOB=shortness of breath.

azithromycin, were used to prevent secondary bacterial infections. Additionally, one study noted the use of immunoglobulins. Corticosteroids were administered in 11 patients. Other drugs used included antiseizure medications. One study reported the empirical use of aspirin (in 80 [85%] of 94 patients) and pentoxifylline (in 79 [84%] of 94 patients) during a Malaysian outbreak, to prevent thrombosis. 15 papers documented intensive care unit

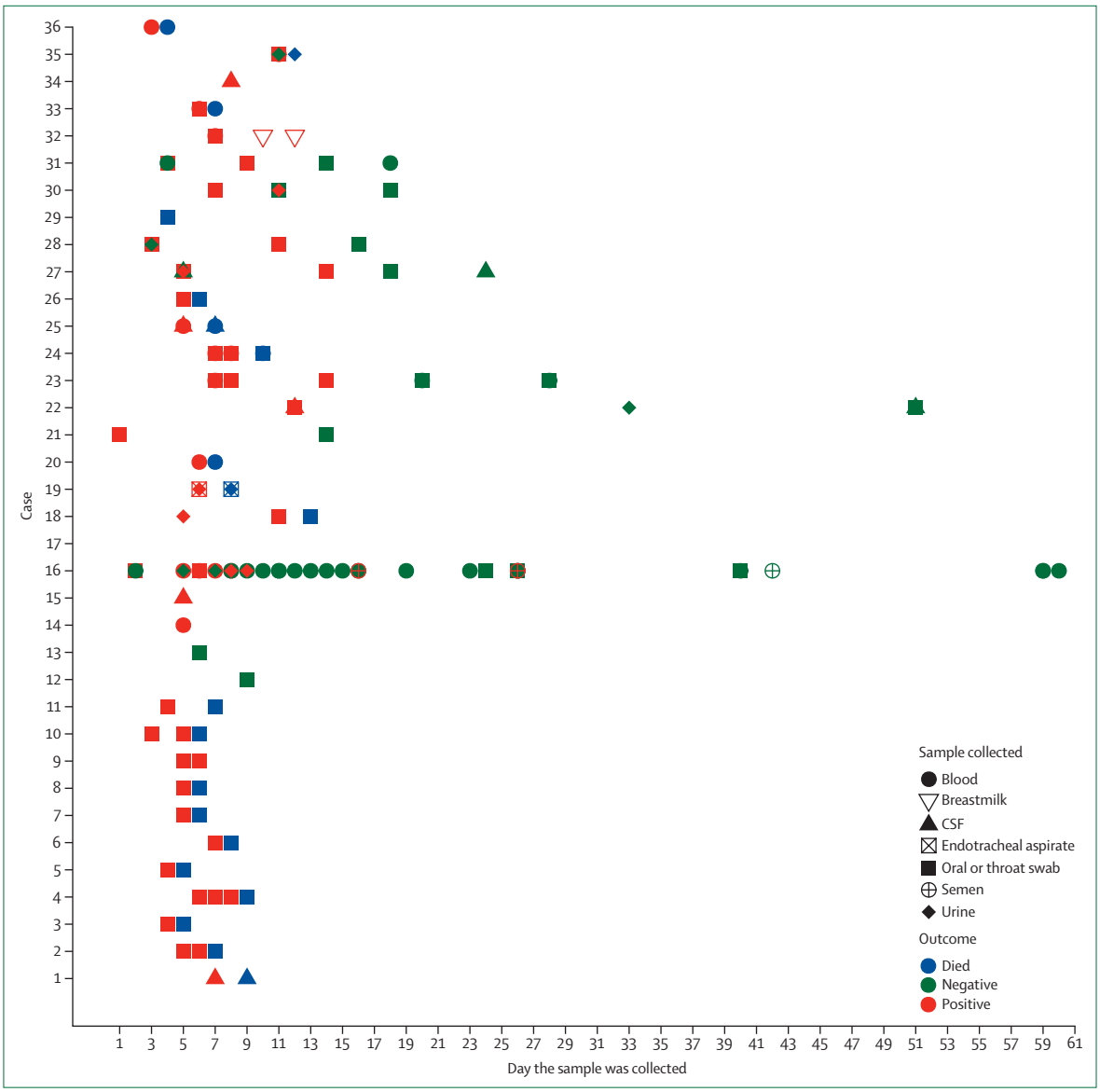

Figure 4: **Nipah virus RNA detections in the body fluids of patients with laboratory-confirmed Nipah virus disease, in relation to days after symptom onset**
CSF=cerebrospinal fluid.

treatment for 189 (54%) of 347 patients. However, in one study from Bangladesh involving 94 cases, only three were treated in the intensive care unit.

Outcomes

Eight studies reported the duration of follow-up, which ranged from 21 to 1460 days. The median CFR was 69% (IQR 31–88%) across the included cohorts (figure 5). The CFR was significantly higher among patients infected with NiV-B than among those infected with NiV-M (70% for NiV-B *vs* 39% for NiV-M; p<0·0001).

Long-term neurological outcomes, defined as any clinical sign or symptom identified after hospital discharge, were reported in 11 publications covering 197 cases with follow-up periods ranging from 1 month to 4 years. Persistent symptoms were present in 69 (35%) of the 197 cases. Neurological deficits were the most common outcome, occurring in 51 (26%) of the 197 cases and included memory disturbance, weakness, ataxia, and optic problems. Psychiatric symptoms, such as severe depressive disorder and personality changes, were reported in six (3%) of the 197 cases. Seizures, resulting in hospital readmission, occurred in five (3%) of the 197 cases.

Risk-of-bias assessments

The studies reported a moderate overall risk of bias. On average, 77% (IQR 70–90%) of the study-specific criteria from the JBI critical appraisal checklists were met across the included studies (appendix pp 25–26).

Discussion

Treatment approaches for NiVD: insights and remaining gaps

This Review identified key differences in the clinical manifestations between the two strains of Nipah virus, particularly a higher prevalence of respiratory symptoms in NiV-B cases. This observation could be attributed to greater pulmonary involvement in NiV-B infections, supported by evidence from animal models that show higher replication of NiV-B in human tracheal and bronchial epithelium and higher viral loads in lung tissues.[64,65] Differences in the predominant route of transmission might also contribute to this observation, with person-to-person and food-borne transmission being more common in NiV-B outbreaks, as compared with the zoonotic transmission via pigs in NiV-M outbreaks. Whether ribavirin treatment during the Malaysian outbreak might have further reduced the proportion of patients with pulmonary involvement is unclear.[66] Respiratory symptoms could also be under-recognised or misclassified in patients with predominant neurological presentations, as they can be mistaken for neurological distress, such as gasping or irregular breathing caused by seizures or altered mental status. This challenge in obtaining a reliable clinical history from critically ill patients could have contributed to differential reporting of respiratory involvement between NiV-M and NiV-B cases.

Respiratory symptoms can also occur early in the disease course, before severe neurological symptoms develop, but are often overshadowed by the severe neurological symptoms at the time of presentation.[65] Gastrointestinal symptoms, such as excessive salivation, were common (44 of 46) but were reported in only one study, which limits interpretation and could reflect selection bias. This finding highlights the need for comprehensive and standardised clinical assessments throughout the disease, to capture the full spectrum and progression of symptoms.

This Review revealed that patients typically presented to the hospital within 3–4 days of symptom onset, with a median illness duration of 22 days for survivors. However, detailed data on the timing of disease progression and how early or late presentation affects outcomes remain scarce. These data are essential for understanding the therapeutic window for interventions and stratifying the affected patients accordingly.

This Review shows that viraemia typically occurs between 4 to 10 days after symptom onset, with the virus detectable in the CNS by day 5 after onset, indicating early CNS involvement. The detection of viral RNA in the CNS and other organs underscores the need for therapeutic agents that can cross the blood–brain barrier and penetrate multiple tissues, to effectively treat the infection. These findings suggest that treatment strategies should prioritise antiviral therapies capable of early administration, particularly during the window of viraemia. This approach could be combined with immune-modulating therapies to reduce inflammation and limit tissue damage across the affected organs. Trials should explore these therapeutic avenues to develop comprehensive treatment strategies for NiVD that address both early viral replication and multiorgan involvement.

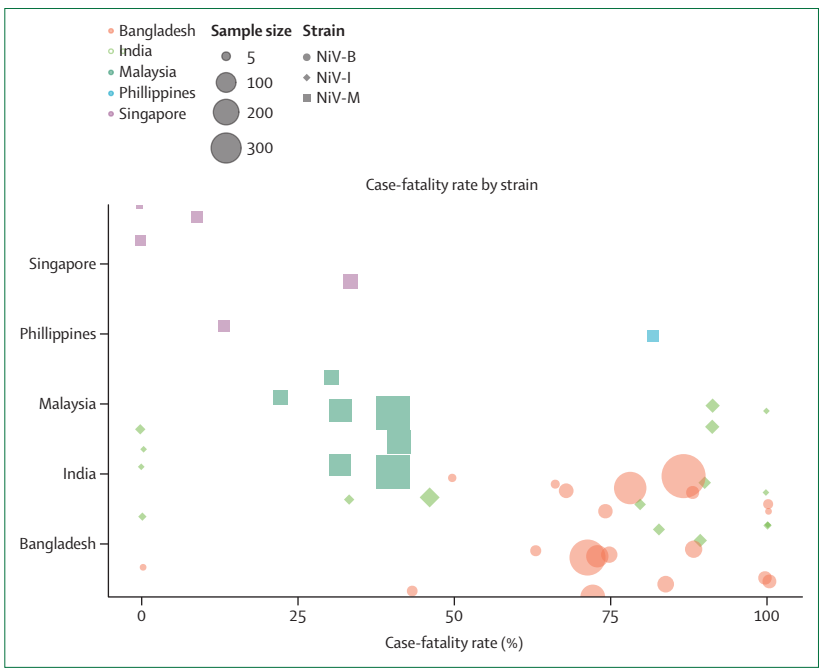

Figure 5: **Case-fatality rate in reported Nipah virus outbreaks by country and NiV strains**
Each dot represents an outbreak, and the size of the dot represents the number of participants. NiV-B=Nipah virus-Bangladesh. NiV-I=Nipah virus-India. NiV-M=Nipah virus-Malaysia.

This Review identified a crucial paucity of autopsy studies on Nipah virus, particularly in Bangladesh, where most cases and deaths occur. This gap, driven by cultural, religious, and biosafety concerns surrounding autopsies,[1,3,67] limits a complete understanding of the key pathophysiological mechanisms. For example, if vasculitis does play an important role in tissue injury,[68] then inflammatory processes might be an important drug target. Although full autopsies are often not feasible in endemic regions due to cultural and biosafety reasons, culturally sensitive alternatives exist. Minimally invasive tissue sampling, already used in Bangladesh, offers a safe and acceptable method for collecting post-mortem data.[69] Verbal autopsies can be useful when tissue collection is not possible, and engaging religious or community leaders can improve local acceptance. Non-invasive imaging, such as portable CT or ultrasound, could also offer insights when available. Additionally, human organoid models are emerging as a promising tool to study Nipah virus pathogenesis in vitro, providing ethically sound alternatives to human autopsy. Future studies should also use animal models to explore strain-specific disease mechanisms.[69]

Assessing the extent of vital organ involvement, such as liver and kidney function, is difficult using current data. For example, although some studies reported elevated liver enzyme concentrations, the severity of these abnormalities

was not reported, making it challenging to determine whether these levels indicate mild dysfunction or severe organ damage. Similarly, imaging data were inconsistent, with varied terminology used across studies. Nonetheless, chest imaging revealed abnormalities in more than 70% of the cases, suggesting a substantial possibility of respiratory involvement, particularly in NiV-B cases. This finding most likely reflects an overestimate, as imaging was presumably conducted in patients with respiratory symptoms. MRI findings showed distinct brain involvement, potentially aiding in differentiating Nipah encephalitis from other causes and informing neurological management.

In this Review, we provide a foundation for informing future clinical trials, in addition to highlighting key data gaps that need to be addressed to optimise trial design.

Case confirmation

The Review identified the absence of a standardised case definition for NiVD, which has implications for both diagnosis and trial enrolment. Historically, case definitions have focused on neurological symptoms, such as encephalitis, often accompanied by fever.[15,44,70] However, the findings of this Review reveal a broader range of presenting symptoms, including gastrointestinal symptoms (eg, excessive salivation and anorexia) and respiratory involvement, particularly in NiV-B outbreaks. This finding highlights that current case definitions might overlook patients who primarily present with respiratory symptoms, as seen in the 2023 outbreaks in Kerala, India and the 2014 outbreak in the Philippines. As shown during the Ebola virus disease epidemic, reliance on narrow case definitions can bias the case mix and diagnostic pathways. For instance, during the outbreak in west Africa, fever was the sole criterion for screening and testing, despite evidence showing that approximately 10% of patients with Ebola virus disease do not present with fever.[71–73] Such restrictive case definitions risk excluding atypical presentations, leading to underdiagnosis and misrepresentation of the true spectrum of the disease.

Expanding the case definition to include multiorgan involvement could increase the sensitivity for identifying suspected cases, leading to faster access to diagnostics and early interventions, which are essential for clinical trials. However, unless these broader definitions are followed with access to rapid diagnostics, clinical trials risk enrolling patients without this infection. Subclinical or asymptomatic infection has been reported in some settings; however, since the focus of this Review is on acute clinical disease to inform therapeutic trials, we did not analyse these cases. The occurrence of subclinical or asymptomatic infection is more relevant to prevention (prophylactic) trials in close contacts, wherein rapid identification or enrolment and appropriate endpoints are crucial.

Predictors of adverse outcomes

Predictors of poor prognosis varied between the included manuscripts. Increasing age consistently correlated with worse outcomes, whereas only one study identified comorbid diabetes as being linked to adverse outcomes. Additionally, patients who succumbed to the disease were more likely to have detectable Nipah virus RNA in oral swabs and cerebrospinal fluid. Although these findings suggest that multiorgan involvement or high viral loads, or both, might be strongly associated with an increased risk of mortality, other important prognostic factors are not yet understood and have the potential to confound findings of clinical trials. Stratification of randomisation by age, sex, disease phenotype, and severity might be required in clinical trial design, or subgroup analyses might be informative.

In particular, comorbidity data were rarely reported, making it difficult to assess how underlying conditions, such as chronic respiratory or cardiovascular disease, might influence prognosis. Of note, data were not available on whether the frequency of adverse outcomes differs by disease phenotype (eg, CNS only *vs* CNS plus respiratory involvement) at presentation.

Baseline standard of care

The Review highlighted substantial disparities in supportive care across the outbreak settings, with higher access to intensive care in Malaysia and Singapore than in Bangladesh and India. These disparities in access to optimal supportive care might have contributed to the observed differences in CFRs, with NiV-M cases having a CFR of 39%, as compared with the 70% for NiV-B cases. However, this difference warrants further investigation, as it might also be influenced by factors such as the route of inoculation or pathogenic differences between the two strains, as shown in animal models.[64]

Additionally, individual-level data on the proportion of patients receiving antivirals, antibiotics, steroids, or oxygen supplementation were inconsistently reported, making it difficult to assess the full impact of supportive care on outcomes. Such data are essential for clinical trials to establish a consistent standard of care and to develop hypotheses about the effectiveness of aspects of supportive care.

The absence of uniform clinical management guidelines across the affected regions highlights the need for evidence-based supportive care protocols. Developing such protocols, akin to WHO's evidence-based guidelines for Ebola virus,[73] would ensure optimal patient care and enable more reliable comparisons of new treatments in clinical trials.

Outcome measures

This Review identified mortality as the most frequently reported outcome in NiVD studies. However, data on other key outcomes, such as organ dysfunction and long-term neurological sequelae, were scarce. Although an average of 35% of survivors in some studies reported persistent neurological deficits,[24,47,52,57] the timing and progression of these sequelae were not consistently documented. Similarly, data on the frequency, severity, and timing of organ

dysfunction, such as liver or kidney impairment, were insufficient.

Understanding the frequency and timing of these outcomes is essential to adequately power prospective trials. Furthermore, trials would be informed by further understanding the duration of post-acute complications, to understand whether interventions can modify these outcomes, which are often of real significance to the affected individuals.

Standardisation of data collection and reporting

Tools exist to prevent inconsistent and incomplete reporting of clinical and laboratory data across studies. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)–WHO Clinical Characterisation Protocol, which was successfully used during the COVID-19 pandemic, provides a useful model. These case-reporting forms are standardised to enable subsequent comparison or amalgamation of data; driven by experts, to ensure that clinical or laboratory features that could be of prognostic value are examined in enough breadth and depth; and are freely available from the start of the outbreak, meaning that detailed prospective data collection is possible—rather than accumulating data from clinical notes, standardised forms capture detailed clinical information.[74]

These tools would be best harnessed in prospective observational studies in endemic regions of south Asia and southeast Asia, particularly Bangladesh and India, where cases occur annually, such as the BASE cohort study.[7]

Defining target product profiles and regulatory pathways

With improved clinical understanding of the disease, an opportunity exists to refine use cases and target product profiles for diagnostics, vaccines, and therapeutics.[2] Priorities for therapeutics include rapid onset of action, CNS penetration, and practical delivery in low-resource settings, given the findings of this Review. These efforts are already underway: in April, 2025, Coalition for Epidemic Preparedness Innovations (CEPI), Indian Council of Medical Research (ICMR), and ISARIC convened a workshop in New Delhi, India, to define use cases and target product profiles for Nipah countermeasures and align them with outbreak scenarios. Although beyond the scope of this Review, innovative trial designs and alternative regulatory pathways, including adaptive protocols, the US Food and Drug Administration's Animal Rule, and emergency-use mechanisms, will be essential to operationalise target product profiles into viable development and deployment strategies.[2,75,76]

Conclusions

The Review highlights missed opportunities to generate reliable evidence on the clinical features of NiVD due to inadequate and incomplete data, paucity of individual-level patient data, inconsistency in reporting, and lack of agreed-upon terminology. The Review underscores the need for a coordinated research response across affected countries with harmonised research methods and universally applicable research tools, to support the development and optimisation of clinical trials for potential treatments.

Contributors

MZH, PH, and PO conceptualised the research problem. MZH wrote the review protocol, developed the search strategy, and conducted the database search under the supervision of EH. MZH and SKI piloted the review process and screened the studies and extracted, analysed, and tabulated the data. MZH drafted and revised the initial manuscript. AR, PO, and PH provided supervision, feedback, and critical review of the scientific content, in addition to editing the draft. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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