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Original Research Article

Nipah Virus Encephalitis and the Medico Legal Brain: Neuropathology, Neurobehavioural Sequelae, Capacity, and One Health Forensics.

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Abstract: ***Background:*** Nipah virus encephalitis is a highly lethal zoonotic infection capable of producing acute cerebral dysfunction, delayed neurological disease, and persistent neurobehavioural impairment; however, its implications for legal capacity, forensic pathology, and One Health investigation remain poorly integrated.A scoping review was conducted according to JBI methodology and reported it in accordance with PRISMA ScR. MEDLINE, Embase, Scopus, Web of Science, APA PsycINFO, CINAHL, Global Health, CAB Abstracts, WHO Global Index Medicus, the Cochrane Library, and relevant grey literature sources were searched from inception through July 2026. Of 624 records identified, 146 duplicates were removed, 478 titles and abstracts were screened, 77 full texts were assessed, and 15 primary studies were included. Methodological quality was evaluated with design specific JBI instruments, the SYRCLE tool for animal studies, and AMSTAR 2 for systematic reviews. The evidence showed that Nipah virus encephalitis involves a combined neurovascular and neurotropic process characterized by endothelial infection, necrotizing vasculitis, thrombosis, microinfarction, parenchymal necrosis, and direct neuronal involvement. Acute disease was associated with altered consciousness, seizures, focal deficits, brainstem dysfunction, and high mortality. Survivors exhibited persistent fatigue, memory and attentional deficits, depression, personality change, behavioural disturbance, impaired mobility, and reduced functional independence; relapsed or late onset encephalitis was documented after apparent recovery. Outbreak investigations further demonstrated occupational, household, caregiving, and health care associated transmission, emphasizing the forensic importance of exposure reconstruction, molecular confirmation, infection control, and evidentiary continuity. No included study directly assessed decisional, testamentary, financial, or criminal capacity. The evidence was limited by small and overlapping cohorts, retrospective designs, inconsistent neuropsychological assessment, incomplete premorbid data, and sparse lesion specific behavioural correlation. Nipah virus may injure neural systems governing memory, judgement, behaviour, and autonomy; nevertheless, neuropathology establishes a biological substrate, not a legal conclusion. Medico legal attribution must remain individual, time specific, function specific, and supported by convergent clinical, cognitive, imaging, pathological, and collateral evidence.

Keywords: Encephalitis, Viral; Forensic Medicine; Henipavirus Infections; Mental Competency; Neurobehavioral Manifestations; Neuropathology; Neuropsychology; Nipah Virus; One Health..

INTRODUCTION

Nipah virus occupies an uncommon and deeply consequential position at the intersection of emerging infection, neuropathology, behavioural medicine, public health, and law. It is not merely a zoonotic pathogen capable of producing fulminant encephalitis; it is a biologically complex agent whose effects may traverse vascular endothelium, cerebral parenchyma, cognition, personality, functional independence, and, ultimately, the legal interpretation of human behaviour. First recognised during the 1998 outbreak among pig farmers in Malaysia, Nipah virus has subsequently caused outbreaks in Singapore, Bangladesh, India, and the Philippines, with recurrent spillover continuing across South and Southeast Asia. Its estimated case fatality rate ranges from 40% to 75%; no licensed antiviral treatment or vaccine is currently available for routine clinical use, and severe disease may progress rapidly from fever and altered sensorium to seizures, brainstem dysfunction, coma, and death [1,2]. These characteristics have rightly positioned Nipah virus among the World Health Organization priority pathogens; yet its significance extends beyond mortality. The infected brain may recover incompletely, relapse after apparent convalescence, or survive with impairments that alter memory, reasoning, emotional regulation, judgement, communication, and social function [1,3].

The neuropathological identity of Nipah virus encephalitis is defined by an unusual convergence of systemic vasculopathy and direct parenchymal infection. Classical autopsy studies demonstrated endothelial injury, necrotising vasculitis, multinucleated endothelial syncytia, thrombosis, vascular occlusion, microinfarction, and focal parenchymal necrosis, with particularly severe involvement of the central nervous system [4]. Viral antigen may be demonstrable within vascular endothelium, neurons, and other parenchymal cells, supporting a pathogenesis in which haematogenous dissemination, endothelial tropism, blood brain barrier disruption, ischaemic injury, and direct neuroinvasion coexist rather than operate as mutually exclusive mechanisms [4]. Neuroimaging provides a living correlate of this microscopic process. Disseminated punctate and small confluent lesions within the subcortical and deep white matter, cerebral cortex, brainstem, and other regions have been interpreted as radiological expressions of small vessel vasculopathy, microinfarction, and focal encephalitic injury [5]. The resulting cerebral disorder is therefore not anatomically uniform; it is a multifocal, temporally evolving injury capable of disrupting distributed networks responsible for arousal, memory, executive control, affective modulation, language, and purposeful behaviour.

This neuropathological heterogeneity has direct implications for the interpretation of neurobehavioural symptoms. During acute disease, reduced consciousness, confusion, agitation, seizures, focal neurological deficits, abnormal brainstem reflexes, and rapid neurological deterioration may obscure the distinction between deliberate conduct and behaviour generated by a severely diseased brain [2,3]. A patient who appears uncooperative, disorganised, emotionally labile, impulsive, or incapable of following instructions may be experiencing encephalopathy, focal network dysfunction, postictal disturbance, hypoxia, cerebral microvascular injury, or evolving encephalitis. Conversely, the presence of Nipah virus infection cannot itself establish that every contemporaneous action was involuntary or cognitively unmediated. The medico legal problem is therefore one of disciplined causal attribution: whether a demonstrable cerebral lesion affected the specific mental function required for a particular act, decision, statement, refusal, consent, or omission at the relevant time. Diagnosis alone is insufficient; temporal proximity, disease severity, neurological examination, neuroimaging, electrophysiology, laboratory confirmation, medication exposure, systemic physiology, premorbid function, and alternative causes must be integrated before any inference concerning cognition or volitional control is advanced.

The legal significance of Nipah associated brain injury becomes even more pronounced among survivors. Early follow up studies documented persistent neurological deficits, psychiatric illness, cognitive impairment, loss of employment, functional dependence, and reduced social participation after acute Nipah encephalitis [6,7]. Depression, changes in behaviour, impaired concentration, memory disturbance, fatigue, and deficits detected through formal neuropsychological assessment have been described, although the available cohorts remain small and geographically concentrated [7,8]. More recent evidence has reinforced the long shadow of infection. A 2026 systematic review and meta analysis identified substantial residual neurological morbidity among survivors, together with a measurable risk of relapsing or late onset neurological disease [9]. Contemporary survivor cohorts have further reported persistent difficulties involving memory, concentration, sleep, mobility, fatigue, and everyday functioning, sometimes many years after the original illness [10]. These findings challenge the binary language of survival and death. Biological survival does not necessarily imply cognitive restoration; discharge from hospital does not establish recovery of executive capacity; and functional independence in elementary daily activities does not exclude subtle but legally relevant impairment in judgement, appreciation, planning, impulse regulation, or complex decision making.

Nipah virus is also remarkable for its capacity to reappear within the nervous system after apparent recovery. Relapsed encephalitis following a recognised acute episode, and late onset encephalitis following

initially asymptomatic or nonencephalitic infection, have both been documented. In a landmark follow up study, recurrent neurological disease developed months after the initial outbreak; patients presented with seizures, focal deficits, headache, and acute encephalitic symptoms, while postmortem examination in selected cases demonstrated focal encephalitis with Nipah viral antigen within the brain [6]. This phenomenon complicates retrospective medico legal reconstruction. A person may have resumed work, entered contracts, provided statements, executed financial instruments, consented to procedures, or participated in legal proceedings before delayed neurological deterioration became clinically evident. The existence of latent or persistent infection does not retrospectively invalidate every preceding decision; nevertheless, it demands careful attention to prodromal cognitive change, contemporaneous behaviour, medical documentation, collateral history, and the possibility that subtle cerebral dysfunction preceded overt relapse. Nipah encephalitis therefore creates a rare temporal problem in forensic medicine: the biological event may begin before its legal relevance becomes visible.

Capacity constitutes one of the most important, yet least examined, dimensions of this disease. Medical and legal capacity is task specific, decision specific, and time specific. It cannot be inferred solely from a diagnostic label, an abnormal magnetic resonance image, or a low score on a cognitive screening instrument. The accepted clinical framework evaluates whether an individual can communicate a choice, understand relevant information, appreciate how that information applies to personal circumstances, and reason among available alternatives [11]. Nipah associated deficits in attention, memory encoding, language, executive function, emotional regulation, and insight could compromise one or several of these abilities; however, the effect must be demonstrated rather than presumed. The relevant question is not simply whether the patient has encephalitis, but whether the documented neuropathology and neuropsychological phenotype impaired the precise mental operation required by the decision under scrutiny. This distinction is essential in the assessment of informed consent, refusal of treatment, testamentary capacity, financial competence, occupational fitness, guardianship, vulnerability during questioning, and the reliability of statements obtained during acute or residual cerebral dysfunction.

The medico legal inquiry does not end with the survivor. Fatal Nipah virus infection presents formidable challenges for forensic pathology, death certification, postmortem sampling, occupational safety, and evidentiary interpretation. Conventional autopsy may provide indispensable information concerning vasculitis, thrombosis, microinfarction, encephalitis, pulmonary injury, and multiorgan viral dissemination; yet manipulation of unfixed tissues from a suspected high consequence pathogen creates substantial biological risk. Histopathology, immunohistochemistry, molecular detection, serology, clinical history, and epidemiological linkage must therefore be interpreted as complementary layers of evidence. A positive molecular result does not automatically establish that infection caused death, while a negative result from an inadequately selected, degraded, or inappropriately handled specimen cannot reliably exclude disease. Recent postmortem surveillance programmes have demonstrated that minimally invasive sampling and molecular testing of deceased patients may identify otherwise unrecognised Nipah virus infection and strengthen outbreak detection [12]. Within legal medicine, such approaches acquire an additional obligation: specimen identity, collection chronology, containment, documentation, chain of custody, analytical validity, and concordance between molecular findings and pathological lesions must be preserved with the same rigour applied to any other evidentiary material.

Nipah virus further resists interpretation within the boundaries of human medicine alone. Pteropus fruit bats constitute the principal natural reservoir; transmission has occurred through contaminated food, infected domestic or bridging animals, and direct contact between people, particularly within households and health care environments [1,13]. The causal narrative of a Nipah death may consequently begin far from the mortuary or hospital: within a bat roost, an orchard, a date palm sap collection site, a livestock enclosure, a market, a household caregiving network, or a health care facility. One Health forensics may therefore be understood as the disciplined reconstruction of this multispecies and environmental chain of events. Human clinical specimens, animal surveillance, viral genomics, food and environmental sampling, contact histories, geographic information, occupational exposure, and pathological findings together form a distributed body of evidence [13,14]. This reconstruction is not undertaken merely to identify where infection originated; it may determine institutional responsibility, occupational exposure, failures of infection control, the legality and proportionality of quarantine measures, compensation claims, public health accountability, and the prevention of secondary transmission.

Despite the biological severity of Nipah virus, its neuropathological, neurobehavioural, legal, and One Health literatures remain insufficiently integrated. Existing studies have principally addressed acute clinical manifestations, outbreak epidemiology, pathological mechanisms, imaging abnormalities, transmission, or survivor morbidity as separate domains. The evidentiary bridge between a lesion and a behaviour, between cognitive impairment and legal capacity, between postmortem detection and causal attribution, or between zoonotic reconstruction and institutional responsibility remains comparatively

underdeveloped. This gap invites two opposite errors: neurological determinism, in which infection is presumed to explain behaviour without functional evidence; and diagnostic neglect, in which disturbed conduct, unreliable communication, or impaired judgement is interpreted without adequate consideration of organic brain disease. A scientifically defensible framework must reject both. It must neither convert cerebral injury into an indiscriminate legal excuse nor permit legal analysis to proceed as though neuropathology were irrelevant.

Accordingly, this scoping review maps the neuropathological architecture, acute and enduring neurobehavioural manifestations, cognitive and psychiatric sequelae, capacity related implications, postmortem considerations, and One Health forensic dimensions of Nipah virus encephalitis. It further examines the degree to which existing evidence can support causal conclusions concerning cognition, behaviour, decision making, functional competence, and death; identifies methodological and geographical limitations within the available literature; and proposes a structured interface between neuropathology, neuropsychology, forensic medicine, clinical ethics, and outbreak investigation. The central premise is exacting but necessary: when infection alters the brain, medicine must establish what changed; when that change enters a legal question, forensic analysis must establish whether it mattered, how it mattered, and with what degree of evidentiary certainty..

METHODOLOGY

Review Design and Reporting Framework

This scoping review was conducted in accordance with the JBI methodological guidance for scoping reviews and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Extension for Scoping Reviews, PRISMA ScR. The literature search and its documentation were additionally structured in accordance with the PRISMA Extension for Searches, PRISMA S.

A scoping review design was selected because the evidence concerning Nipah virus encephalitis extended across heterogeneous clinical, neuropathological, neuroradiological, neuropsychological, psychiatric, forensic, veterinary, epidemiological, and One Health domains. The review was therefore designed to map the extent, characteristics, methodological quality, and medico legal relevance of the available literature, rather than to estimate a single pooled effect.

Review Question

The principal review question was:

What neuropathological, neurobehavioural, cognitive, and psychiatric abnormalities have been reported during or after Nipah virus encephalitis, and how may these findings inform medico legal assessment, decisional capacity, postmortem diagnosis, and One Health forensic investigation?

Eligibility Criteria

Eligibility was defined through the Population, Concept, and Context framework recommended by JBI for scoping reviews.

The population included children and adults with laboratory confirmed, epidemiologically linked, clinically probable, or postmortem confirmed Nipah virus infection. Eligible clinical presentations included acute encephalitis, encephalopathy, relapsed encephalitis, late onset encephalitis, residual neurological disease, and fatal infection. Survivors without documented acute encephalitis were also eligible when subsequent neurological, cognitive, psychiatric, behavioural, or functional abnormalities were reported and were plausibly related to Nipah virus infection.

Animal and experimental studies were included only when they directly informed human neurotropism, cerebral vasculopathy, neuronal infection, viral persistence, routes of neuroinvasion, neuropathological distribution, behavioural dysfunction, postmortem detection, or One Health forensic reconstruction.

The concepts of interest included encephalitis, encephalopathy, cerebral endothelial injury, vasculitis, thrombosis, microinfarction, haemorrhage, neuronal infection, gliosis, inflammation, parenchymal necrosis, and blood brain barrier dysfunction. Neurobehavioural and functional outcomes included altered consciousness, confusion, agitation, seizures, memory impairment, executive dysfunction, impaired attention, language disturbance, personality change, emotional dysregulation, psychosis, depression, anxiety, sleep disturbance, fatigue, occupational impairment, and functional dependence.

Medico legal concepts included decisional capacity, informed consent, refusal of treatment, testamentary capacity, financial competence, guardianship, occupational fitness, vulnerability during questioning, reliability of statements, postmortem diagnosis, cause of death attribution, specimen integrity, biosafety, and chain of custody. One Health concepts included reservoir identification, zoonotic spillover, environmental exposure, animal transmission, health care associated transmission, genomic epidemiology, outbreak reconstruction, and institutional responsibility.

No geographical, age related, occupational, or health care setting restrictions were applied.

Sources of Evidence

Eligible evidence included prospective and

retrospective cohort studies, case control studies, cross sectional studies, outbreak investigations, survivor follow up studies, diagnostic studies, autopsy series, neuropathological studies, case series, case reports, qualitative studies, mixed methods studies, and translationally relevant animal studies.

Systematic reviews and meta analyses were examined separately and were used to identify additional primary studies. Government reports, outbreak reports, public health guidance, technical documents, biosafety recommendations, policy statements, theses, conference proceedings, and preprints were eligible when they contained sufficient methodological or outcome information.

Editorials, narrative commentaries, opinion pieces, news reports, unsourced internet material, and publications without extractable Nipah virus specific findings were excluded. Studies concerning Hendra virus or other henipaviruses were excluded unless Nipah virus data were reported separately.

Information Sources

Electronic searches were conducted in MEDLINE through PubMed, Embase, Scopus, Web of Science Core Collection, APA PsycINFO, CINAHL, Global Health, CAB Abstracts, WHO Global Index Medicus, and the Cochrane Library.

Supplementary searches were undertaken in HeinOnline and Google Scholar to identify medico legal, ethical, policy, and grey literature sources. Relevant documents were also sought through the World Health Organization, the Centers for Disease Control and Prevention, the Food and Agriculture Organization, the World Organisation for Animal Health, national ministries of health, public health agencies, institutional repositories, and official outbreak investigation platforms.

The databases were searched from inception through July 2026. No publication date restriction was applied. No language restriction was imposed during the initial search. Non English publications were evaluated where reliable translation was available.

The reference lists of included studies and relevant reviews were examined manually. Forward citation tracking was performed through Scopus, Web of Science, and Google Scholar.

Search Strategy

The search combined controlled vocabulary and free text terms representing Nipah virus infection, neurological injury, neuropathology, cognition, behaviour, forensic medicine, legal capacity, postmortem investigation, and One Health.

The core search structure included:

"Nipah virus" OR "Nipah henipavirus" OR "Nipah infection" OR NiV

Combined with:

encephalitis OR encephalopathy OR neurological OR neuropsychiatric OR neuropsychological OR cognition OR memory OR executive function OR behaviour OR psychiatric OR personality OR capacity OR competence OR consent OR forensic OR medico legal OR autopsy OR postmortem OR neuropathology OR vasculitis OR vasculopathy OR thrombosis OR infarction OR brain OR biosafety OR One Health OR zoonosis OR outbreak investigation

The strategy was adapted to the indexing structure and syntax of each database. Database specific search strategies, search dates, and numbers of retrieved records were documented in the supplementary material.

Study Selection

The electronic database search identified 589 records. Citation tracking, grey literature searches, institutional repositories, reference list screening, and supplementary searches yielded an additional 35 records, resulting in a total of 624 potentially relevant records. After 146 duplicate records were removed, 478 unique titles and abstracts underwent screening against the predefined Population, Concept, and Context criteria.

During title and abstract screening, 401 records were excluded. These records were removed because they did not concern Nipah virus infection; addressed other viral, neurological, or zoonotic diseases without separately extractable Nipah virus data; focused exclusively on virology, therapeutics, vaccination, or general epidemiology without relevant neurological, neuropathological, neurobehavioural, forensic, or One Health outcomes; or represented clearly ineligible publication types without usable primary evidence. Seventy seven reports were considered potentially eligible and were therefore retrieved for detailed full text assessment.

Following independent full text evaluation, 62 reports were excluded. Seventeen reports contained no extractable Nipah virus specific data, including publications in which Nipah virus findings were combined with those of other henipaviruses or emerging infections without separate analysis. Sixteen reports did not provide outcomes relevant to neurological disease, neuropathology, cognition, behaviour, psychiatric manifestations, functional capacity, forensic interpretation, postmortem investigation, or One Health reconstruction. Nine publications were reviews, commentaries, editorials, or opinion articles that did not contain eligible primary evidence. Eight reports represented duplicate publications or substantially overlapping outbreak cohorts without additional

extractable outcomes and were excluded to prevent repeated representation of the same participants. Six reports lacked sufficient methodological detail, diagnostic confirmation, participant characteristics, outcome definitions, or extractable results to permit reliable evidence charting. A further six animal studies were excluded because their findings did not provide direct translational information regarding human neuroinvasion, neuropathology, neurobehavioural dysfunction, postmortem diagnosis, or forensic interpretation.

Fifteen primary studies satisfied all eligibility criteria and were included in the final qualitative evidence synthesis. Titles and abstracts were screened independently by two reviewers, after which the same reviewers independently assessed the full texts of potentially eligible reports. Disagreements were resolved through discussion and consensus; where consensus could not be reached, a third reviewer adjudicated the final decision. No reports were unavailable for retrieval, and no records were excluded through automated screening tools. The complete process of study identification, screening, eligibility assessment, exclusion, and final inclusion is presented in the PRISMA 2020 flow diagram in Figure 1 [35].

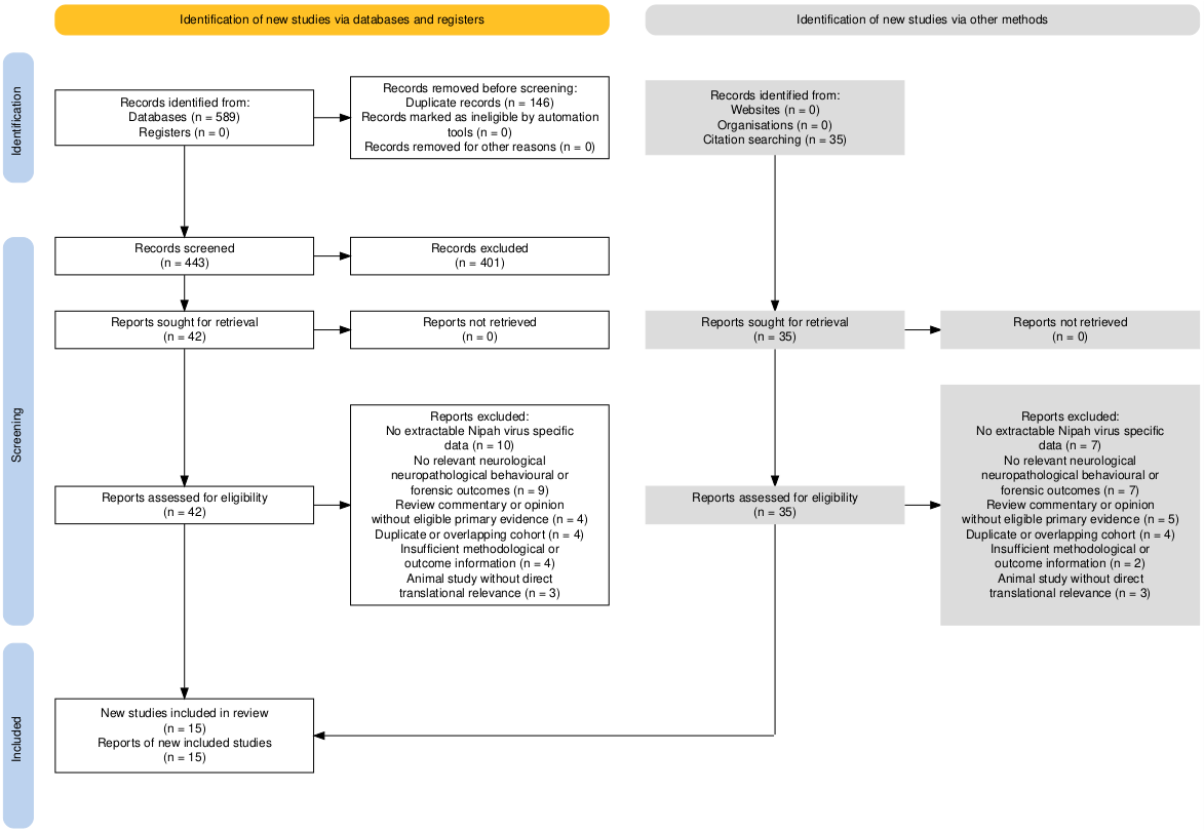

Figure 1: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of studies. A total of 624 records were identified, including 589 records retrieved from electronic databases and 35 additional records obtained through citation searching and grey literature sources. After the removal of 146 duplicate records, 478 records underwent title and abstract screening, of which 401 were excluded for failing to meet the predefined population, concept, or context criteria. Seventy seven full text reports were subsequently retrieved and assessed for eligibility. Sixty two reports were excluded because they contained no extractable Nipah virus specific data, n = 17; lacked relevant neurological, neuropathological, behavioural, or forensic outcomes, n = 16; were reviews, commentaries, or opinion articles without eligible primary evidence, n = 9; represented duplicate or substantially overlapping cohorts, n = 8; contained insufficient methodological or outcome information, n = 6; or involved animal studies without direct translational relevance, n = 6. Fifteen primary studies fulfilled all eligibility criteria and were included in the final qualitative synthesis. No reports were unavailable for retrieval, and no records were excluded through automated screening tools.

Data Extraction and Evidence Charting

A standardized data charting form was developed and piloted before formal extraction. One reviewer extracted the data, while a second reviewer independently verified the principal study characteristics, pathological findings, neurological outcomes, neurobehavioural manifestations, and medico legal interpretations.

The following variables were extracted where available:

1. Author, publication year, country, outbreak, study setting, and study design.
2. Sample size, age distribution, sex distribution, occupation, and route of exposure.
3. Definition and certainty of Nipah virus infection.
4. Serological, molecular, virological, immunohistochemical, or genomic confirmation.
5. Acute neurological manifestations and level of consciousness.
6. Neuroimaging modality, lesion distribution, and temporal evolution.
7. Neuropathological findings, including endothelial injury, vasculitis, thrombosis, microinfarction, haemorrhage, inflammation, neuronal infection, gliosis, and necrosis.
8. Cognitive, psychiatric, behavioural, and functional outcomes.
9. Neuropsychological instruments and the cognitive domains assessed.
10. Premorbid cognitive, psychiatric, occupational, and social function.
11. Duration of follow up, residual disability, return to work, functional dependence, relapse, late onset encephalitis, and mortality.
12. Evidence relating to understanding, appreciation, reasoning, communication of choice, judgement, insight, and behavioural control.
13. Autopsy method, postmortem interval, specimen selection, tissue fixation, molecular testing, immunohistochemistry, biosafety procedures, and cause of death formulation.
14. Animal, environmental, genomic, occupational, and epidemiological evidence relevant to One Health reconstruction.
15. Funding sources, conflicts of interest, missing data, and study limitations.

Legal incapacity, diminished responsibility, or impaired volitional control was not inferred solely from the presence of Nipah virus infection, encephalitis, abnormal neuroimaging, or psychiatric symptoms. Medico legal implications were charted only when explicitly reported or when supported by sufficiently detailed functional evidence.

Risk of Bias and Methodological Quality Assessment

Risk of bias and methodological quality were formally assessed because the review sought not only to map the available literature, but also to determine the strength with which cerebral pathology could be associated with cognition, behaviour, legal capacity, and cause of death.

Two reviewers independently appraised each included study using a design appropriate instrument. Disagreements were resolved through consensus or adjudication by a third reviewer.

Human observational studies were assessed using the relevant JBI critical appraisal checklists. Cohort studies were evaluated for participant selection, exposure measurement, identification and management of confounding variables, outcome ascertainment, follow up completeness, and statistical analysis.

Cross sectional studies were assessed for clearly defined eligibility criteria, adequate description of participants and settings, valid exposure and outcome measurement, identification of confounding variables, and appropriateness of statistical analysis.

Case control studies were assessed for comparability of cases and controls, validity of case and control identification, exposure measurement, management of confounding variables, and consistency of outcome ascertainment.

Case series were evaluated for explicit inclusion criteria, reliable diagnostic methods, consecutive or complete participant inclusion, adequate reporting of demographic and clinical characteristics, outcome ascertainment, and statistical methods.

Case reports were assessed for clarity of demographic information, clinical chronology, diagnostic procedures, therapeutic interventions, postintervention condition, adverse events, and the interpretation of clinical findings.

Diagnostic accuracy studies were evaluated for participant selection, conduct and interpretation of the index test, appropriateness of the reference standard, participant flow, and timing between diagnostic procedures.

Qualitative studies were assessed using the JBI checklist for qualitative research. Experimental animal studies were evaluated using the SYRCLE risk of bias tool, which examines selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential methodological limitations.

Eligible systematic reviews were assessed using AMSTAR 2 and were mapped separately from the primary evidence.

Each appraisal item was classified as yes, no, unclear, or not applicable, according to the specifications of the relevant instrument. Arbitrary numerical quality scores were not calculated because the included studies represented methodologically distinct evidence designs.

Studies were not excluded solely because they demonstrated high or unclear risk of bias. Such exclusion would have removed important evidence concerning a rare and geographically restricted infection. Nevertheless, studies with substantial methodological limitations were not permitted to support strong causal, clinical, legal, or policy conclusions.

The study level risk of bias judgements and the distribution of methodological concerns across the principal appraisal domains are presented in Figure 2. The most frequent concerns involved participant selection, inadequate control of confounding variables, incomplete longitudinal assessment, and insufficient correlation between neuropathological abnormalities and specific neurobehavioural outcomes. Nevertheless, diagnostic certainty and objective neurological outcome measurement were generally adequate in the principal clinical, neuroradiological, and neuropathological studies.

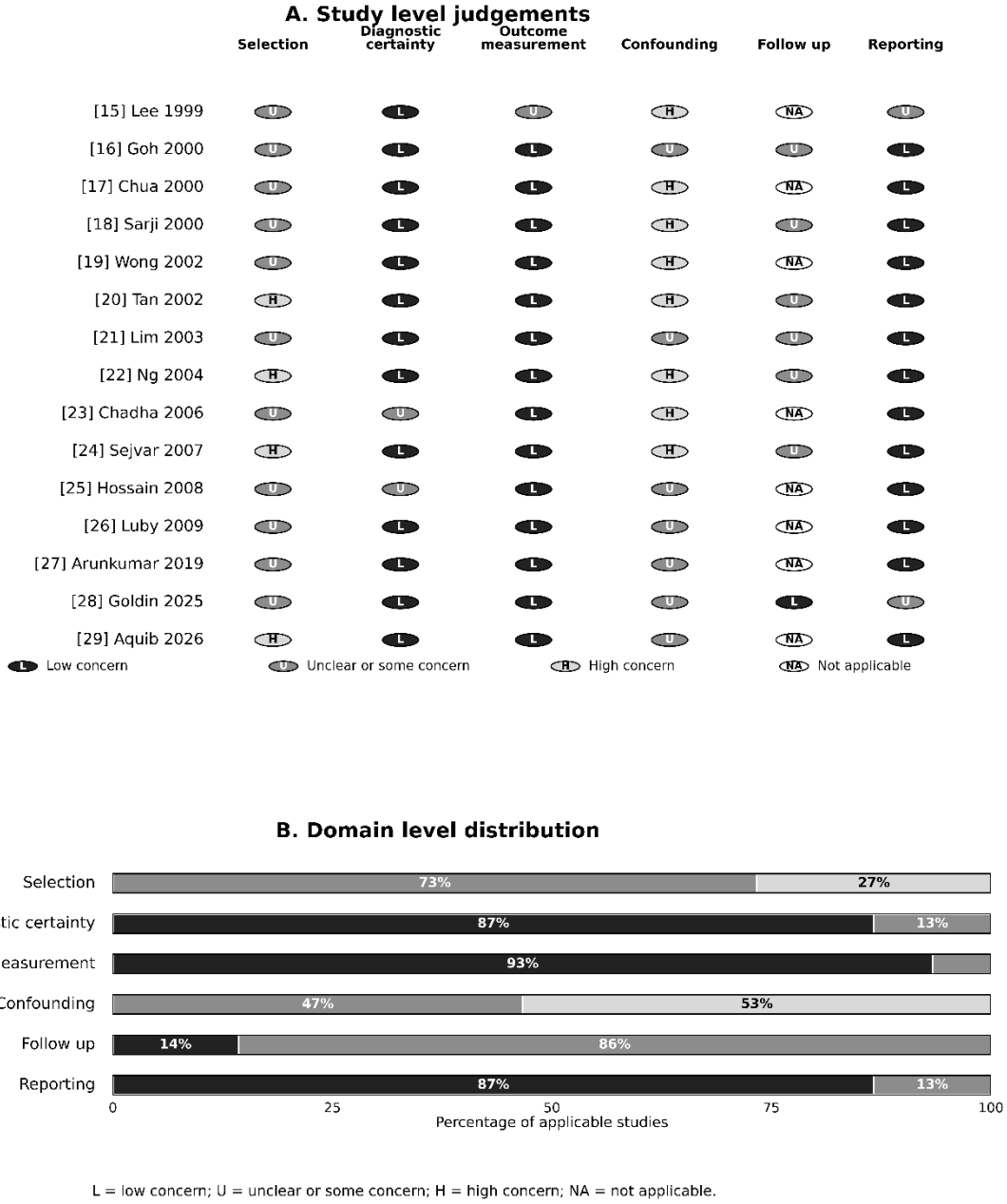

Figure 2: Methodological quality and risk of bias across the included studies. Study level judgements are presented through a greyscale traffic light matrix, with the distribution of concerns across the principal methodological domains shown alongside. Human studies were evaluated through design appropriate JBI criteria, whereas the experimental animal study was interpreted using SYRCLE principles.

Forensic Causal Interpretability

A supplementary forensic causal interpretability framework was applied because conventional risk of bias tools do not establish whether a specific cerebral lesion caused a particular cognitive, behavioural, or medico legal impairment.

The framework examined diagnostic certainty; objective evidence of central nervous system involvement; temporal concordance between cerebral dysfunction and the behaviour or decision under examination; anatomical and functional plausibility; documentation of premorbid cognitive and psychiatric function; exclusion of hypoxia, metabolic disturbance, medication effects, intoxication, delirium, and postictal states; use of validated neurological, cognitive, psychiatric, or functional assessment; availability of collateral or documentary corroboration; and consistency among clinical, imaging, pathological, molecular, and behavioural findings.

For postmortem evidence, additional consideration was given to specimen integrity, postmortem interval, contamination control, analytical validation, tissue selection, and maintenance of chain of custody.

The framework was not converted into a numerical legal responsibility score. Its purpose was to distinguish biological association from functionally demonstrated impairment and to prevent unsupported movement from diagnosis to incapacity, behavioural causation, or legal exculpation.

Evidence Synthesis

The included evidence was synthesized descriptively and thematically. Study characteristics were summarized through frequencies, proportions, medians, ranges, structured tables, and evidence maps where appropriate.

The findings were organized into the following domains:

1. Viral neuroinvasion and cerebral vasculopathy.
2. Neuropathological and neuroradiological distribution.
3. Acute neurological and neurobehavioural manifestations.
4. Persistent cognitive, psychiatric, behavioural, and functional sequelae.
5. Relapsed and late onset encephalitis.
6. Decisional capacity, competence, vulnerability, and functional decision making.
7. Autopsy pathology, molecular confirmation, and cause of death attribution.
8. Biosafety, specimen integrity, and evidentiary continuity.
9. Reservoirs, transmission pathways, genomic linkage, and One Health forensic reconstruction.
10. Methodological limitations and research priorities.

Meta-analysis was not undertaken because substantial heterogeneity was present across study populations, outbreak settings, diagnostic definitions, pathological methods, neuropsychological instruments, follow up durations, and reported outcomes.

Interpretive confidence was determined through the convergence of methodological quality, diagnostic certainty, directness, consistency, temporal coherence, objective cerebral evidence, and functional correlation.

Ethical Considerations

The review used published and publicly accessible evidence and did not involve direct interaction with human participants or access to identifiable individual level information. Institutional ethical approval was therefore not required.

RESULTS

Characteristics of the Included Evidence

Fifteen primary studies published between 1999 and 2026 were included in the final synthesis [15 - 29]. Fourteen studies investigated human Nipah virus infection, whereas one evaluated neuropathological changes in an African green monkey model [28]. The evidence comprised acute clinical studies, neuropathological and neuroradiological investigations, survivor follow up cohorts, outbreak reconstructions, and experimental neuropathology. Several Malaysian and Singaporean reports examined different outcomes within partially overlapping outbreak populations; therefore, cumulative participant numbers were not combined [15 - 22].

Acute Neurological Manifestations

Acute Nipah virus infection was consistently associated with rapidly progressive encephalitis, altered consciousness, seizures, focal neurological deficits, and brainstem dysfunction [15,16]. The Malaysian clinical cohort demonstrated severe neurological deterioration, with prominent signs of brainstem and upper cervical cord involvement [16]. Isolation of Nipah virus from the cerebrospinal fluid was markedly more frequent among fatal than nonfatal cases, supporting an association between direct central nervous system viral involvement and mortality [17].

Clinical presentations varied across outbreaks. Bangladeshi patients frequently developed encephalitis together with cough, respiratory distress, and severe systemic disease [25]. The 2018 Kerala outbreak was characterized by rapidly progressive neurological illness, frequent respiratory manifestations, extensive contact related transmission, and very high mortality [27].

Neuropathology and Neuroimaging

Neuropathological examination revealed widespread endothelial infection, necrotizing vasculitis, thrombosis, vascular

occlusion, microinfarction, focal parenchymal necrosis, and direct neuronal infection [19]. Magnetic resonance imaging commonly demonstrated multiple punctate or small confluent lesions involving the subcortical and deep white matter, cerebral cortex, and brainstem, consistent with a multifocal vasculopathic and encephalitic process [18].

Relapsed and late onset encephalitis showed a distinct temporal and radiological pattern, with seizures, focal neurological deficits, and cortical lesions developing months after apparent recovery [20,21]. Comparable vascular, inflammatory, and parenchymal abnormalities were reproduced in the African green monkey model, including neuropathological lesions in animals without overt neurological symptoms [28].

Neuropsychiatric and Functional Sequelae

Persistent cognitive and psychiatric abnormalities were documented among survivors. Formal neuropsychological evaluation demonstrated substantial impairment in attention, verbal memory, and visual memory, with verbal memory frequently more severely affected [22]. Long term follow up in Bangladesh identified persistent fatigue, neurological dysfunction, behavioural change, delayed neurological abnormalities, and reduced functional independence [24].

Relapsed or late onset encephalitis occurred after an interval of apparent recovery and was associated with seizures, focal deficits, cortical inflammation, and additional mortality [20]. The most recent Bangladeshi survivor cohort confirmed that neurological, physical, cognitive, and functional impairments may persist for several years following acute infection [29].

One Health and Medico Legal Findings

The included outbreak investigations demonstrated multiple transmission pathways. The Malaysian outbreak was principally associated with occupational exposure to infected pigs [15 to 19]. The Siliguri outbreak showed extensive transmission within a hospital environment [23], whereas recurrent Bangladeshi outbreaks reflected repeated zoonotic introductions together with occasional person to person transmission [26]. The Kerala outbreak further demonstrated the importance of close caregiving contact, exposure to respiratory secretions, and failures in early infection recognition [27].

These findings support the medico legal relevance of occupational history, institutional infection control, exposure reconstruction, molecular confirmation, and continuity of epidemiological evidence [23,26,27]. However, none of the included studies directly assessed testamentary, financial, criminal, or treatment related legal capacity. The medico legal implications were therefore inferred cautiously from documented disturbances in consciousness, memory, executive function, behaviour, judgement, and functional independence [20,22,24,29].

The distribution of evidence across the clinical, neuropathological, neuroradiological, neuropsychiatric, cognitive, functional, transmission, and One Health domains is summarized in Figure 3. Acute neurological disease, virological confirmation, transmission pathways, and neuropathological mechanisms were comparatively well represented. In contrast, systematic cognitive assessment, long term functional evaluation, and direct medico legal assessment remained sparse. None of the included studies directly evaluated decisional capacity, testamentary competence, financial competence, criminal responsibility, or fitness to participate in legal proceedings.

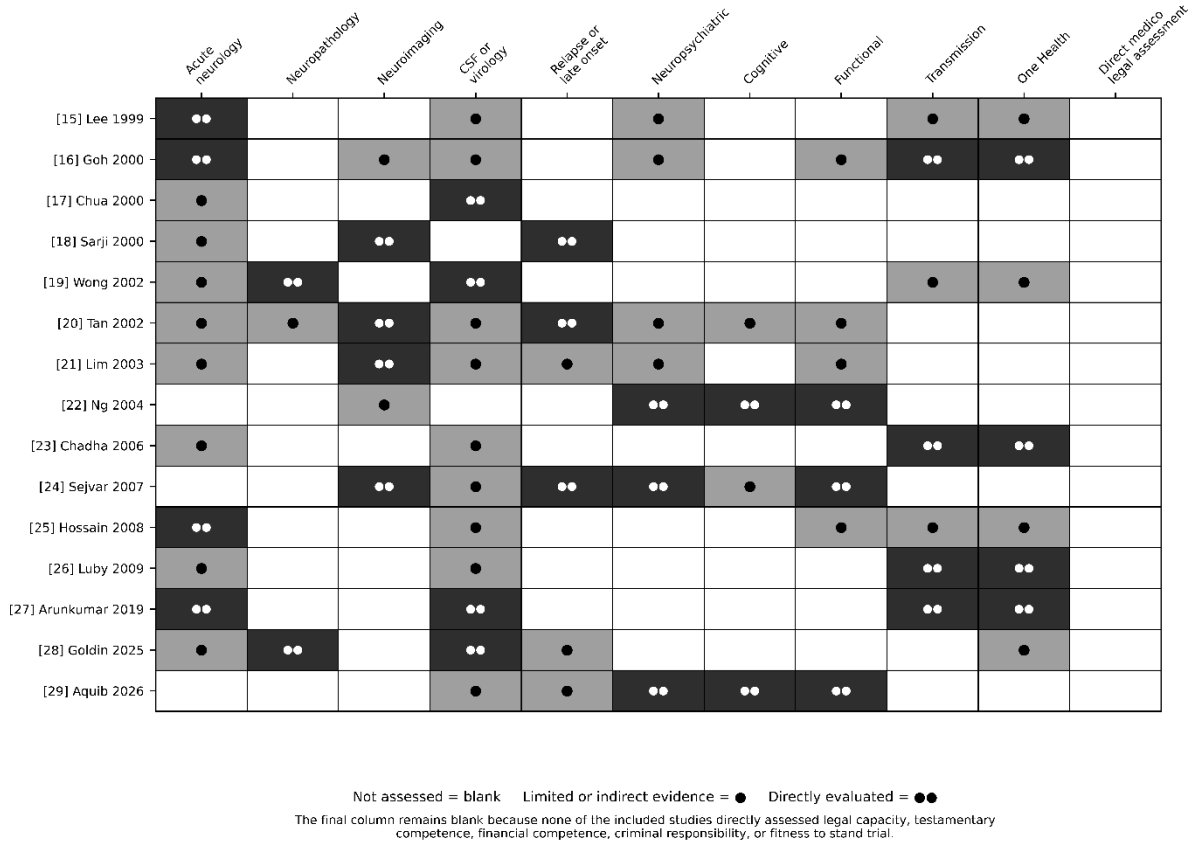

Figure 3: Evidence map across the fifteen included studies. The map demonstrates the clinical, pathological, neurobehavioural, functional, transmission, and One Health domains directly or indirectly evaluated within each study. The absence of evidence within the direct medico legal assessment column identifies the principal unresolved gap in the literature.

Methodological Quality

The evidence base was limited by small samples, retrospective designs, overlapping outbreak cohorts, incomplete premorbid cognitive information, inconsistent neuropsychological testing, limited comparator groups, and heterogeneous follow up periods [15 - 29]. Neuropathological and neuroradiological studies provided strong evidence of structural and vascular cerebral injury; however, direct correlations between lesion location, specific behavioural disturbance, and legal incapacity remained insufficient.

Accordingly, the available evidence supported a biologically plausible association between Nipah virus encephalitis and persistent neurobehavioural dysfunction, but did not justify deterministic attribution of incapacity, impaired responsibility, or legally relevant behaviour to infection alone.

The cumulative findings are summarized in Table 1. below.

Table 1. Characteristics and Principal Findings of the Fifteen Included Studies

Reference	Setting, design, and study population	Principal findings	Relevance to the present review
Lee et al., 1999 [15]	Singapore; descriptive clinical neurological series of patients with Nipah virus encephalitis	Neurological involvement was diverse and multifocal, including aseptic meningitis, diffuse encephalitis, cerebellar dysfunction, and focal brainstem involvement.	Established the principal acute neurological phenotype and demonstrated that Nipah virus may disrupt several functionally important cerebral and brainstem networks.
Goh et al., 2000 [16]	Malaysia; observational clinical cohort of **94 patients**, predominantly pig	Fever, headache, dizziness, vomiting, reduced consciousness, segmental myoclonus, areflexia, and brainstem	Demonstrated severe acute encephalitis, occupational exposure, rapid neurological

	farmers	signs were prominent. Thirty patients died, producing a mortality rate of **32%**.	deterioration, and the potential for profound impairment of consciousness and purposeful behaviour.
Chua et al., 2000 [17]	Malaysia; retrospective virological analysis of cerebrospinal fluid from **84 patients**, comprising 27 fatal and 57 nonfatal cases	Nipah virus was isolated from the cerebrospinal fluid of **17 of 27 fatal cases**, compared with **1 of 57 nonfatal cases**.	Supported an association between direct central nervous system viral involvement and mortality, strengthening biological attribution in severe and fatal disease.
Sarji et al., 2000 [18]	Malaysia; magnetic resonance imaging study of **31 patients** with acute, relapsed, or late onset encephalitis	Acute disease produced multiple discrete lesions, measuring approximately 2 to 7 mm, predominantly in the subcortical and deep cerebral white matter. Relapsed and late onset disease showed more confluent cortical involvement.	Provided radiological correlates of multifocal vasculopathy, microinfarction, and delayed cortical injury.
Wong et al., 2002 [19]	Malaysia; clinicopathological and autopsy study of **32 fatal human cases**	Systemic endothelial infection, necrotizing vasculitis, thrombosis, vascular occlusion, microinfarction, focal parenchymal necrosis, and direct neuronal infection were demonstrated.	Established the dual mechanism of vascular injury and direct neuronal infection that underpins the neuropathological interpretation of Nipah encephalitis.
Tan et al., 2002 [20]	Malaysia and Singapore; clinical and neuroradiological series of **22 patients** with relapsed or late onset encephalitis	Neurological disease appeared after an average interval of approximately **8.4 months**. Seizures, focal neurological deficits, headache, fever, and cortical magnetic resonance abnormalities were frequent; four patients died.	Demonstrated that neurological disease may emerge or recur after apparent recovery, complicating retrospective assessment of cognition, behaviour, and functional capacity.
Lim et al., 2003 [21]	Singapore; clinical and magnetic resonance follow up of **22 affected individuals**, including 13 encephalitis survivors and 9 asymptomatic seropositive workers	Most cerebral lesions remained stable or improved; however, residual cranial nerve palsy, depression, retinal artery occlusion, spinal cord involvement, and small cerebral lesions in asymptomatic individuals were identified.	Showed that clinically silent or residual nervous system injury may remain after the acute infection and may not be captured by routine functional assessment alone.
Ng et al., 2004 [22]	Singapore; prospective neuropsychiatric follow up of **9 encephalitis survivors** over 24 months	Eight patients developed psychiatric manifestations. Depression, personality change, and chronic fatigue were reported. Seven of eight formally tested patients had substantial deficits in attention and verbal or visual memory.	Supplied the most direct evidence linking Nipah encephalitis with persistent psychiatric symptoms, memory impairment, attentional dysfunction, and personality alteration.
Chadha et al., 2006 [23]	Siliguri, India; retrospective outbreak investigation involving **66 probable cases**	Forty five patients died. The clustering of illness among health care workers, hospital patients, and visitors provided strong evidence of hospital associated person to person transmission.	Established the forensic importance of exposure reconstruction, institutional infection control, occupational risk, and hospital transmission.
Sejvar et al., 2007 [24]	Bangladesh; long term neurological and functional follow up of **22 survivors**	All but one survivor reported disabling fatigue. Seven had persistent neurological dysfunction, four developed delayed neurological abnormalities, and magnetic resonance abnormalities were detected in 15. Behavioural changes were frequent among younger survivors.	Demonstrated prolonged neurological morbidity, behavioural disturbance, delayed dysfunction, and impairment of everyday functioning after survival.

Hossain et al., 2008 [25]	Bangladesh; clinical analysis of **92 patients** identified across four outbreaks	Sixty seven patients died. Fever, altered mental status, headache, cough, respiratory difficulty, vomiting, and convulsions were prominent, demonstrating combined neurological and respiratory disease.	Showed that behavioural and cognitive assessment during acute infection may be confounded by severe systemic illness, respiratory failure, hypoxia, and rapidly progressive encephalopathy.
Luby et al., 2009 [26]	Bangladesh; epidemiological analysis of **122 recognized cases** arising from 23 separate viral introductions between 2001 and 2007	Eighty seven patients died. Fifty one percent developed illness after close contact with another infected person, although onward transmission was concentrated among a limited number of cases. Respiratory difficulty increased transmission risk.	Demonstrated repeated zoonotic spillover followed by selective person to person transmission, supporting a combined epidemiological and One Health forensic approach.
Arunkumar et al., 2019 [27]	Kerala, India; clinical, molecular, genomic, and epidemiological outbreak investigation of **23 cases**, including 18 laboratory confirmed cases	Twenty one patients died, yielding a case fatality rate of **91%**. Respiratory symptoms occurred in 87%. Close physical contact, nursing, and exposure to infected secretions were major transmission risks.	Highlighted the importance of molecular confirmation, contact tracing, hospital infection control, occupational exposure, and reconstruction of transmission chains.
Goldin et al., 2025 [28]	Experimental primate neuropathology study involving **14 African green monkey brains** with Nipah virus associated lesions	Viral RNA and antigen were identified in neurons and endothelial cells, both within encephalitic lesions and in apparently uninvolved cerebral tissue. Perivascular inflammation, vascular necrosis, glial nodules, parenchymal loss, and CD8 positive and CD68 positive inflammatory responses were demonstrated.	Reproduced key features of human neuropathology and showed that viral persistence and cerebral injury may occur in regions lacking overt inflammation or obvious neurological signs.
Aquib et al., 2026 [29]	Bangladesh; cross sectional assessment of **52 adult Nipah virus survivors**	Persistent symptoms included sleep disturbance in 58%, gait disturbance in 54%, memory or concentration difficulty in 54%, chronic fatigue in 52%, and myoclonus in 48%. Functional impairment was particularly evident in anxiety, mobility, and cognition.	Confirmed that neurological, cognitive, psychiatric, and physical morbidity may persist for years and may affect independence, occupational function, and complex decision making.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; NiV, Nipah virus.

Several Malaysian and Singaporean publications examined different clinical, imaging, pathological, or follow up outcomes within partially overlapping outbreak populations [15- 22]. Their participant numbers should therefore not be added to produce a cumulative sample size. Furthermore, none of the included studies directly evaluated legal capacity, testamentary capacity, criminal responsibility, or competence to consent. Their medico legal relevance arises from documented abnormalities of consciousness, memory, attention, executive function, personality, behaviour, and functional independence.

DISCUSSION

This review demonstrates that Nipah virus encephalitis is not a uniform inflammatory disorder, but a layered neurovascular disease in which endothelial infection, vasculitis, thrombosis, microinfarction, and direct neuronal invasion converge to produce acute cerebral dysfunction and persistent neurological vulnerability. Early clinical series described encephalitis, altered consciousness, seizures, myoclonus, focal deficits, and brainstem involvement [15,16]. Viral isolation from cerebrospinal fluid was concentrated among fatal cases, reinforcing the relationship between central nervous system viral burden and adverse outcome [17]. Neuroimaging and autopsy findings were complementary: punctate white matter and cortical lesions corresponded to a diffuse small vessel process, whereas histopathology demonstrated endothelial syncytia, vascular necrosis, thrombosis, parenchymal injury, and neuronal antigen [18,19]. The clinical phenotype therefore cannot be reduced either to direct viral cytotoxicity or to systemic encephalopathy alone.

Experimental evidence strengthens this dual

mechanism. Nipah virus can use mononuclear leukocytes as vehicles for dissemination, while infected immature dendritic cells show enhanced migration across human brain microvascular endothelium [30,32]. In hamsters, viral entry through the olfactory epithelium and olfactory bulb demonstrated an additional neural route into the brain [31]. These mechanisms explain why lesion distribution may be multifocal and neurological severity may differ between patients. The primate study further demonstrated inflammatory, vascular, and neuronal abnormalities during acute disease and convalescence, including lesions without obvious neurological signs [28]. Clinically silent pathology must not be equated with incapacity; nevertheless, it warns against assuming that normal bedside interaction excludes residual cerebral injury.

The survivor literature extends this concern beyond hospitalization. Relapsed and late onset encephalitis occurred after apparent recovery, often with seizures, focal deficits, and cortical abnormalities [20,21]. Prospective assessment identified persistent depression, personality change, fatigue, attentional impairment, and deficits in verbal and visual memory [22]. Bangladeshi cohorts similarly documented delayed neurological abnormalities, behavioural change, impaired mobility, fatigue, memory or concentration difficulties, and reduced functional independence [24,29]. Broader encephalitis research confirms that memory, executive, and psychiatric impairments may persist despite substantial physical recovery [34]. These findings support structured longitudinal assessment rather than discharge based solely on apparent recovery.

The medico legal implications are important, but must remain disciplined. None of the included Nipah studies directly evaluated competence to consent, testamentary capacity, financial capacity, criminal responsibility, or reliability under interrogation. Infection, an abnormal magnetic resonance image, or a psychiatric symptom cannot independently establish legal incapacity. The defensible question is functional and time specific: did cerebral disease impair understanding, appreciation, reasoning, memory, judgement, communication, or behavioural control at the relevant moment? Evidence from survivor studies establishes biological plausibility [20,22,24,29], but individual attribution requires contemporaneous examination, neuropsychological testing, collateral history, premorbid comparison, and exclusion of delirium, hypoxia, seizures, metabolic dysfunction, medication effects, and severe emotional distress. This distinction prevents neurological determinism and diagnostic neglect.

The outbreak studies broaden the forensic frame from the individual brain to the chain of transmission. Occupational exposure to pigs shaped the Malaysian outbreak [16], whereas hospital associated spread was central in Siliguri and close caregiving contact was important in Bangladesh and Kerala [23,26,27]. A Bangladeshi case control investigation found that close contact with an infected patient increased infection risk and documented viral contamination of hospital surfaces [33]. Exposure chronology, caregiving practices, respiratory secretions, infection control, and molecular linkage are relevant to occupational liability, preventable transmission, and public health accountability. One Health forensics must integrate human pathology with animal exposure, environmental evidence, contact tracing, and viral genomics.

Taken together, the evidence supports an integrated framework extending from ecological exposure and zoonotic transmission to neurovascular and neuronal injury, acute cerebral dysfunction, persistent neurobehavioural sequelae, and subsequent medico legal questions. These relationships are summarized in Figure 4. A defensible forensic interpretation requires temporal concordance, premorbid comparison, exclusion of competing causes, standardized neuropsychological assessment, clinicoradiological and clinicopathological correlation, molecular confirmation, and preservation of evidentiary continuity. Neuropathology may establish the biological substrate of impairment; it cannot, in isolation, establish legal incapacity, diminished responsibility, or unreliable decision making.

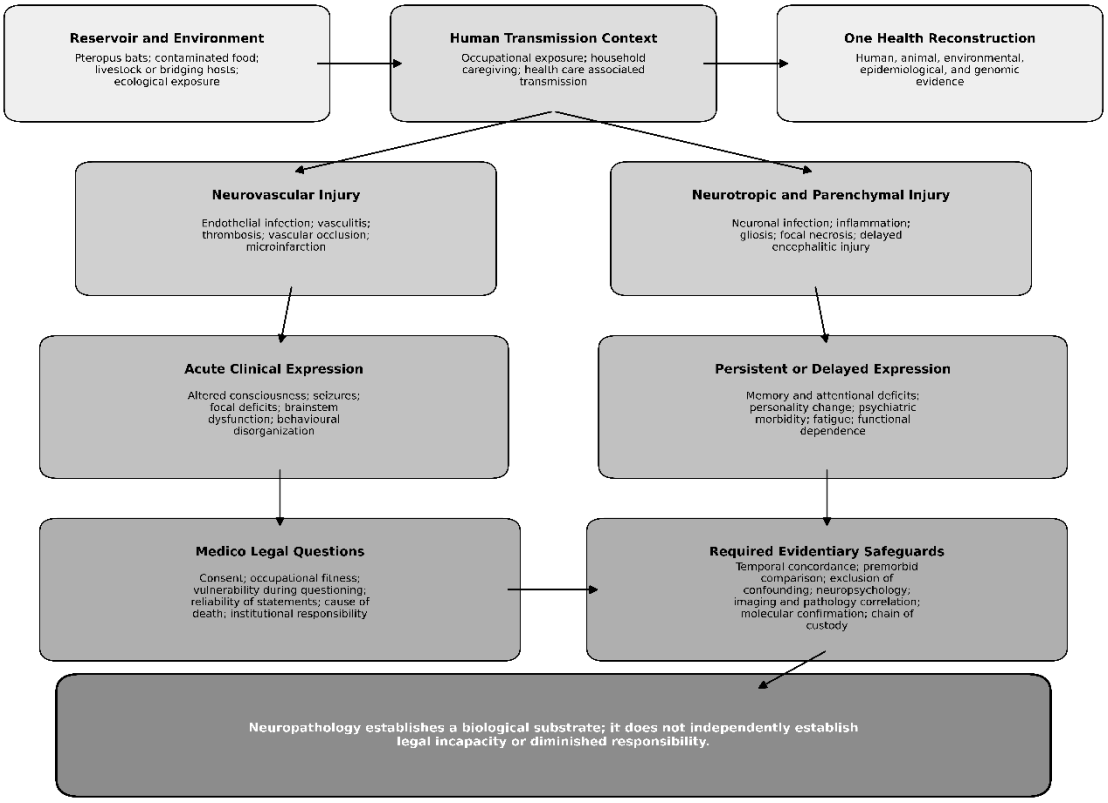

Figure 4: Integrated medico legal and One Health framework for Nipah virus encephalitis. The framework connects reservoir and environmental exposure, human transmission, cerebral vascular and neuronal injury, acute and persistent neurobehavioural manifestations, medico legal questions, and the evidentiary safeguards required for scientifically defensible attribution.

Interpretation remains constrained by concentrated outbreaks, small cohorts, retrospective analyses, overlapping populations, and heterogeneous follow up. Premorbid cognition was seldom documented, neuropsychological batteries were inconsistently applied, and lesion specific behavioural correlations were rare. Autopsy evidence arose mainly from fatal Malaysian disease, while experimental findings cannot be translated directly into legal conclusions about humans. Publication bias toward severe presentations is also probable.

Future studies should establish prospective survivor registries incorporating standardized imaging, psychiatric assessment, domain specific neuropsychological testing, functional capacity measures, and repeated follow up. Autopsy protocols should harmonize cerebral sampling, molecular testing, biosafety, and clinicopathological correlation. Medico legal assessment should be incorporated prospectively rather than reconstructed after dispute. The evidence supports a precise conclusion: Nipah virus can produce enduring injury to neural systems governing memory, affect, judgement, and behaviour; pathology establishes the substrate of impairment, but not the legal conclusion itself.

CONCLUSION

Nipah virus encephalitis represents a complex neurovascular and neurotropic disorder in which endothelial injury, vasculitis, thrombosis, microinfarction, direct neuronal infection, and delayed cerebral inflammation converge to produce acute neurological collapse and, in survivors, persistent cognitive, psychiatric, behavioural, and functional impairment. The available evidence supports a credible biological basis for disturbances in consciousness, memory, attention, judgement, personality, emotional regulation, and independent functioning.

These abnormalities may carry substantial medico legal importance in relation to consent, occupational fitness, vulnerability, reliability of statements, postmortem attribution, institutional responsibility, and One Health outbreak reconstruction. Nevertheless, neuropathology establishes the substrate of impairment, not the legal conclusion itself. Any inference concerning incapacity, diminished control, or responsibility must remain individual, time specific, function specific, and supported by contemporaneous clinical, neuropsychological, imaging, pathological, and collateral evidence.

The conclusions of this review must be interpreted within important limitations. The evidence base was

dominated by small, geographically concentrated outbreak cohorts, several of which partially overlapped; retrospective designs, incomplete premorbid information, inconsistent neuropsychological testing, variable follow up, limited comparator groups, and publication bias toward severe disease further restricted certainty.

Direct assessments of decisional, testamentary, financial, or criminal capacity were absent, while lesion specific correlations with behaviour remained sparse. Autopsy evidence was largely derived from fatal cases, and animal findings, although mechanistically informative, cannot be translated directly into human legal determinations. Future research should therefore prioritize prospective survivor registries, standardized cognitive and psychiatric assessment, harmonized neuropathological sampling, longitudinal imaging, functional capacity testing, and integrated One Health evidence systems. The central conclusion remains precise: Nipah virus may injure the neural systems upon which memory, judgement, behaviour, and autonomy depend; forensic interpretation must determine, with disciplined evidentiary restraint, when that injury became legally meaningful.

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