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Original article

Evaluating the need for standardised disease manifestation categories in patients infected with the tick-borne encephalitis virus: A Delphi panel

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ABSTRACT

Categorization systems for tick-borne encephalitis virus (TBEV) infection lack consistency in classifying disease severity. To evaluate the need for a standard, consensus-based categorisation system for TBEV infection across subtypes, we gathered an expert panel of clinicians and scientists with diverse expertise in TBEV infection. Consensus was sought using the Delphi technique, which consisted of 2 web-based survey questionnaires and a final, virtual, consensus-building exercise. Ten panellists representing 8 European countries participated in the Delphi exercise, with specialities in neurology, infectious disease, paediatrics, immunology, virology, and epidemiology. Panellists reached unanimous consensus on the need for a standardised, international categorisation system to capture both clinical presentation and severity of TBEV infection. Ideally, such a system should be feasible for use at bedside, be clear and easy to understand, and capture both the acute and follow-up phases of TBEV infection. Areas requiring further discussion were (1) the timepoints at which assessments should be made and (2) whether there should be a separate system for children. This Delphi panel study found that a critical gap persists in the absence of a feasible and practical classification system for TBEV infection. Specifically, the findings of our Delphi exercise highlight the need for the development of a user-friendly classification system that captures the acute and follow-up (i.e., outcome) phases of TBEV infection and optimally reflects both clinical presentation and severity. Development of a clinical categorisation system will enhance patient care and foster comparability among studies, thereby supporting treatment development, refining vaccine strategies, and fortifying public health surveillance.

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1. Introduction

The tick-borne encephalitis virus (TBEV) is an enveloped, positive-sense RNA virus that is transmitted to humans by infected ticks (genus *Ixodes*) or, less commonly, by consumption of unpasteurised dairy products from infected animals (Bogovič et al., 2010; Bojkiewicz et al., 2020; Ruzek et al., 2019). TBEV, also known as *Orthoflavivirus* encephalitidis, is neurotropic, and infection often results in febrile illness and can additionally result in neurological manifestations and symptoms (Bogovič et al., 2022; Postler et al., 2023; Ruzek et al., 2019). These include potentially fatal infections of the peripheral nervous system (PNS) and central nervous system (CNS) (Kohlmaier et al., 2021; Ruzek et al., 2019). Tick-borne encephalitis (TBE) is defined by the European Centre for Disease Prevention and Control (ECDC) as any person infected with TBEV with symptoms of inflammation of the CNS or PNS (for example, meningitis, meningoencephalitis, or combinations thereof) and meeting laboratory criteria for case confirmation (e.g., TBE-specific immunoglobulin M and immunoglobulin G antibodies in blood) (European Centre for Disease Prevention and Control, 2024). The incidence of TBE has increased during the last few decades and is a growing health concern in several central, eastern, and northern European countries, such as Germany, Latvia, and Sweden. (European Centre for Disease Prevention and Control, 2024; Kunze et al., 2022). Furthermore, the actual number of TBE cases is likely higher than that reported to public health surveillance, as not all symptomatic cases are medically attended, not all medically attended cases are diagnosed, and not all diagnosed cases are reported to national surveillance systems (Albinsson et al., 2024; European Centre for Disease Prevention and Control, 2022; Granerod et al., 2023; Schley et al., 2023).

There are 3 accepted subtypes of TBEV: the Far Eastern, Siberian, and European subtypes (Bogovič et al., 2010; Dai et al., 2018; Sukhorukov et al., 2023). Two additional, putative subtypes have been reported: the Baikalian and Himalayan subtypes (Dai et al., 2018; Grard et al., 2007; Kovalev and Mukhacheva, 2017). TBEV infections in European countries are predominantly caused by the European subtype; however, other subtypes have been reported to co-circulate in several countries, such as Finland and Latvia (Amicizia et al., 2013; Jääskeläinen et al., 2006; Lundkvist et al., 2002). Compared with Far Eastern or Siberian subtypes, symptoms of infections caused by the European subtype are more likely to follow a biphasic course characterised by non-specific symptoms in the first stage, followed by an asymptomatic interval and a second stage with involvement of the nervous system (Bogovič et al., 2022; Donoso Mantke et al., 2008; Ličková et al., 2021; Ruzek et al., 2019). Disease manifestation and outcomes of TBEV infection can be influenced by a variety of factors, including age, genetic predisposition, concomitant diseases and medication, infection route, or TBEV subtype (Bogovič et al., 2010; Ruzek et al., 2019). The majority of patients with TBE require hospitalisation, and a systematic search conducted by the European Academy of Neurology showed that up to 12 % of hospitalized patients require intensive care unit (ICU) treatment and up to 7 % require artificial ventilation (Taba et al., 2017). Further, the results of a European multicentre study of patients with confirmed TBE—conducted within countries where the European subtype is known to circulate—demonstrated that many patients experience persisting symptoms at discharge, including headache, ataxia, and tremor, and nearly half have been reported to suffer long-term sequelae (Kohlmaier et al., 2021).

Disease manifestations of TBEV infection are reported heterogeneously in the literature. TBEV does not always affect the CNS, but non-CNS cases are difficult to assess as they are not well recognized or reported in official surveillance by the ECDC criteria (Freimane et al., 2024). Some authors categorize nervous system manifestations as meningitis, encephalitis, and encephalomyelitis or radiculitis (stratified by mild, moderate, and severe disease manifestations, respectively) (Santonja et al., 2023; Stähelin-Massik et al., 2008). However, this categorisation system lacks appropriate nuance of disease severity—for instance, meningitis cases are not always mild, especially in children—and does not necessarily overlap with other approaches to disease classification. Other authors relate severity categories to monofocal and multifocal CNS infections (Pichler et al., 2017). Categories based on points on a symptom duration scale have also been developed (Bogovic et al., 2014). This notable variation in categorisation methods for TBEV infection results in a lack of consistency in comprehensive disease severity descriptions and impacts the ability to compare data between studies. Accordingly, we conducted an expert Delphi panel to seek consensus on the requirement and best approach for the development of a clinical categorisation system that captures the clinical presentation and defensible gradients of severity of TBEV infection and is easily useable by a variety of specialists. The focus of this panel was on a categorisation system that could be used across subtypes and for epidemiological purposes rather than to guide treatment pathways.

2. Materials and methods

2.1. Study design and panellists

To seek consensus on the requirement and approach for developing a clinical categorisation system for TBEV infection, we invited European experts representing a broad range of expertise and clinical experience in TBEV infection to participate in a Delphi panel exercise. The Delphi technique—a widely employed iterative process for achieving convergence of opinion—offers the benefit of capturing real-world knowledge from anonymised experts within a given field and incorporates a structured feedback process, which maintains focus and encourages panellists to revisit and reassess their initial judgements (Hsu and Sandford, 2007). To ensure broad consensus-building efforts, panellists with diverse expertise in TBEV infection and its detection and treatment were eligible for study participation (Table 1). Prior to their participation, all panellists provided written informed consent to participate in this study.

In addition to the Delphi panellists, an internationally recognised neurologist and clinical expert in TBE (U.K.M.-L.) was selected as a scientific advisor to oversee the study design and the development of study materials and to ensure the quality of the information gathered. Additionally, the scientific advisor reviewed the results after each phase of data collection and assisted in interpretation of the findings. The advisor did not participate in the Delphi panel exercise and did not make alterations to data collected from the panellists or present personal opinions.

2.2. Delphi panel

The Delphi panel exercise comprised a review of pre-read materials, responses to 2 web-based survey questionnaires, and a final consensus-building exercise (Fig. 1). To enable the panellists to arrive at valid and reliable judgements, panellists were blinded to one another throughout the data collection phase of the study; this was achieved by using participant numbers instead of names and by dissuading the use of cameras during the consensus-building process. The Delphi panel exercise was conducted independently of the study sponsor (i.e., Pfizer) and, whilst the study sponsor was aware of the panellists' identities, the data provided by panellists was not attributable to them. Finally, panellists gave permission to be unblinded to each other upon completion of the survey questionnaires and consensus-building exercise.

Prior to administration of the first survey questionnaire, panellists received pre-read materials that highlighted the varying clinical categorisation systems used for the classification of TBEV infection in the literature. Panellists then completed 2 questionnaires before participating in the consensus-building exercise. The initial questionnaire was developed to summarise panellists' TBEV infection experience and expertise; opinions regarding the classification of clinical manifestations and severity of TBEV infection; and opinions regarding TBEV infection

classification systems for epidemiological purposes. The second questionnaire was designed to summarise results from the initial questionnaire and pose follow-up questions to elicit deeper feedback on the appropriateness of different categorisation systems. The questionnaires and consensus-building exercise focused on TBEV across all subtypes and were not specific to the European subtype. Following analysis of all questionnaire data, we conducted a virtual, anonymised consensus-building exercise, which was focused on outstanding areas of disagreement. The consensus-building exercise was led by an experienced Delphi panel moderator (M.P.), and additional researchers with expertise in qualitative research and moderation (M.G., J.R.) were present to ensure that adequate discussion probes were implemented, that each topic was fully covered, and that all results were reported and confirmed.

Levels of consensus among the 10 panellists were defined as "Complete" (unanimous agreement without qualification by all 10 panellists endorsing a statement), "Strong" (8 to 9 panellists that were in agreement, or 100 % of panellists that were in agreement with minor qualifications), "Moderate" (7 panellists that were in agreement, with or without qualifications), or "Weak" (6 panellists were in agreement). These definitions were used to describe the levels of consensus among panellists' responses to specific questions asked in the survey questionnaires as well as the levels of consensus achieved regarding specific topics that were addressed during the consensus-building exercise.

3. Results

3.1. Panellist characteristics

Ten panellists participated in the Delphi panel exercise (G.D., A.E., G. K., L.K., J.K., J.S., F.S., M.V., J.Z., D.Z.). The panel included neurologists, infectious disease specialists, paediatricians, an immunologist, epidemiologists specialising in infectious disease, and a health scientist specialising in encephalitis (Table 2). Panellists represented European countries including Austria, Czechia, Germany, Latvia, Poland, Slovenia, Sweden, and the United Kingdom. Of the 7 panellists in clinical practice, time in practice ranged from 6 to 10 years to ≥31 years (6–10 years, n = 1; 11–15 years, n = 1; 16–20 years, n = 2; 21–30 years, n = 2; ≥31 years, n = 1). In the past 12 months, one clinical practice panellist had not treated any patients with potential TBE, whilst 2 panellists had treated 1–10 patients, and one panellist each had treated 11–20, 21–30, 31–40, or ≥41 patients with potential TBE, respectively.

3.2. Delphi panel: findings from survey questionnaires 1 and 2

Survey 1 was a broad questionnaire covering existing categorisation systems for TBEV infection and important characteristics of TBEV infection to include in a categorisation system, whilst survey 2 was a targeted questionnaire seeking to explore the appropriateness of different categorisation systems for TBEV infection. In summary, panellists agreed upon the importance of a standardised categorisation system that reflects both clinical presentation and disease severity for TBEV infection (survey 1) and agreed that a two-part (i.e., acute and long-term) categorisation system would be appropriate (survey 2).

3.2.1. The importance of a standardised categorisation system and current categorisation systems

In the initial questionnaire, there was unanimous consensus (n = 10; 100 %) that it is important to have a general standard categorisation system for TBEV infection that reflects both clinical presentation and severity of illness. Panellists indicated that such a system is important to ensure comparability among studies and provide prognostic implications for better understanding the course and severity of the disease, all of which can aid in research, treatment decisions, triaging patients, and public health responses. Panellists also indicated the system should consider both clinical presentation and severity of TBEV infection and should be easy to follow and standardised across countries. The majority of the panellists (n = 8; 80 %) agreed that there is a general standard categorisation system that reflects the severity of illness, whilst fewer panellists agreed that there is a general standard categorisation system that reflects the clinical presentation of symptomatic TBEV infection (n = 4; 40 %) or both clinical presentation and severity of illness (n = 3; 30 %).

Results of the second questionnaire revealed unanimous consensus that TBEV infection has both acute and long-term impacts on patients and that a two-part disease manifestation categorisation system for symptomatic TBEV infection—one for the acute phase for clinical use and the second for follow-up and outcomes—would be appropriate. In survey 2, panellists were presented with 3 types of categorisation systems for both the acute and follow-up phases based on those reported in the literature. The options presented to panellists for acute disease manifestation categorisation were based on clinical measurements (e.g., eye movement, brainstem reflexes); a points system (e.g., points assigned on the basis of the presence of signs and symptoms and their duration); or clinical manifestations and neurological findings (e.g., fever, headache, confusion, seizures) (Barp et al., 2020; Bogovic et al., 2014; Dobler et al., 2020; Lim et al., 2019; Patel et al., 2012; Pustijanac et al., 2023; Rankin, 1957; van Ettekoven et al., 2019). Options presented for follow-up disease manifestations were based on disability and function (e.g., unable to walk unassisted); progression and remission over time (e.g., neurological sequelae or mild disabilities beyond 6 months); and progression, remission, and impact on daily life (e.g., persistent symptoms, some interference with daily activities) (Bogovič et al., 2018; Günther et al., 1997; Patel et al., 2012; Rankin, 1957; van Ettekoven et al., 2019). The survey results showed varying degrees of support, feasibility, and clarity for each categorisation system (Table 3). Notably, 80 % of panellists agreed with the general approach, clarity, and bedside feasibility of acute systems based on clinical measurements, but only 60 % agreed with their ability to adequately capture clinical

Table 1
Panellist eligibility criteria.

Inclusion criteria
TBEV infection expert based in northern, central, or eastern Europe
Clinical specialist in neurology or infectious diseases, with extensive expertise in TBE and/or experience in diagnosing and managing patients with TBEV infection
Or Epidemiologist or public health specialist with expertise in infectious diseases and a deep understanding of data categorisation and real-world data
Or Infectious disease methodologist with extensive expertise in categorising infectious disease data
Or Member of a TBE or TBE-related NGO with demonstrated knowledge of TBE and its treatment
Ability to read, speak, and understand English
Willingness and ability to provide informed consent
Willingness and ability to complete 2 web-based Delphi questionnaires
Ability to engage in a remote, web-based group interview
Exclusion criteria
Inability to read, speak, and understand English
Inability to provide informed consent
Inability to engage in a web-based group interview at the time of recruitment

NGO = non-governmental organisation; TBE = tick-borne encephalitis, TBEV = tick-borne encephalitis virus.

presentation or severity. Regarding follow-up disease manifestation categorisation, 80 % of panellists supported and agreed with the general approach of systems based on disability and function, 80 % supported and 90 % agreed with the general approach of systems based on progression and remission (long-term impacts), whilst only 60 % of panellists supported or agreed with the approach of systems based on progression or remission and impact on daily life.

3.2.2. Consideration of meningitis, encephalitis, and myelitis; monofocal and multifocal presentations; and additional clinical manifestations

Following the exploration of the importance of a standardised categorisation system considering both clinical presentation and disease severity of TBEV infection, the survey 1 and 2 questionnaires asked panellists about 2 systems existing at present: meningitis, encephalitis, and myelitis; and monofocal and multifocal presentations. Results from the initial questionnaire showed strong consensus among panellists (n = 9; 90 %) that meningitis, encephalitis, and myelitis should be considered in a categorisation system for the clinical manifestation of TBEV infection. Rationale for agreement included the clinical phenotypes and diagnostics currently used in clinical practice, the need for clear criteria to guide appropriate treatment, and clinical differences between these conditions. Rationale for opposition to the consideration of these 3 conditions included variability of the severity and impact of these conditions and criticisms of the categorisation system, with panellists specifically noting the possibility of patient death in all 3 categories and questioning the ability of the system to adequately capture the severity and potential outcomes of TBEV infection.

Additionally, in the initial questionnaire, 50 % of panellists (n = 5) supported a categorisation system for patients infected with TBEV using the categories "mild," "moderate," and "severe" based on whether the patient has meningitis, encephalitis, or myelitis. Panellists in support noted the importance of a clearly defined categorisation system for a more precise downstream clinical assessment of disease severity and emphasised that defined categorisation in meningitis, encephalitis, and myelitis would be an improvement over subjective, severity-based classification. However, 40 % of panellists (n = 4) disagreed and 10 % (n = 1) expressed uncertainty, noting that this type of categorisation may not provide the desired level of precision for clinical assessment of disease severity. Panellists also described challenges related to this type of categorisation system, including difficulties in defining criteria for mild, moderate, and severe classifications; difficulties in distinguishing between these categories; and the potential for varying degrees of severity within forms of meningitis and encephalitis.

In the initial questionnaire, there was moderate consensus among panellists on the inclusion of monofocal and multifocal presentations in a categorisation system for the clinical manifestation of TBEV infection, with agreement among 70 % of panellists (n = 7), disagreement among 20 % of panellists (n = 2), and uncertainty for 10 % of panellists (n = 1). Rationale for agreement included the value of these descriptors in assessing and classifying disease severity, clinical presentations, outcomes, and prognosis. Panellists specifically noted that characterising manifestations as monofocal or multifocal provides insights into the severity of TBEV infection in specific regions or over different time periods, and this system indicates potential variations in clinical presentations and related complications. Rationale for disagreement included the rare condition of monofocal presentation and the challenges and complexity in interpreting multifocal symptoms, as most conditions are not straightforward and typically involve multiple symptoms or manifestations.

Finally, panellists were asked to provide any additional clinical manifestations that should be considered in a categorisation system.

Table 2
Panellist characteristics.

Characteristic	n
Specialty	
Clinical practice	7
Infectious disease	2
Paediatric infectious disease	2
Neurology	2
Immunology	1
Epidemiology	2
Non-governmental organisation	1
Country	
Czechia	2
Sweden	1
Poland	1
Austria	1
Germany	1
Latvia	2
Slovenia	1
UK	1
Credentials	
MD, PhD	7
MD, MBA	1
MD	1
PhD	1
Time in practice (post residency, clinical practice specialty only) (N = 7), years	
6–10	1
11–15	1
16–20	2
21–30	2
≥31	1
Patients treated with potential TBEV infection (past 12 months, clinical practice specialty only) (N = 7)	
0	1
1–10	2
11–20	1
21–30	1
31–40	1
≥41	1

TBE = tick-borne encephalitis; TBEV = tick-borne encephalitis virus; UK = United Kingdom.

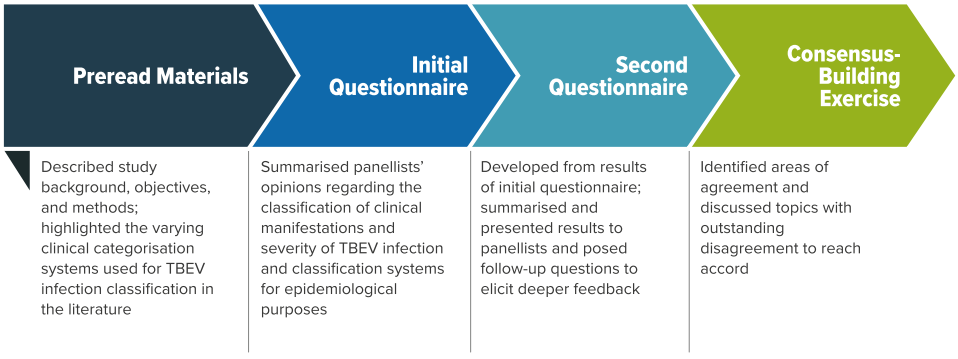

Fig. 1. Delphi panel study design.
TBE = tick-borne encephalitis.

Table 3
Panellist opinions regarding different types of acute and follow-up disease manifestation categorisation systems.

Acute disease manifestation categorisation			
Based on	Clinical measurements[a-d]	Points system[e]	Clinical manifestations and neurological findings[f-h]
Support (as is or with modifications)	50 %	70 %	50 %
Agree with the general approach	80 %	60 %	80 %
Feasibility at bedside	80 %	60 %	60 %
Adequately captures clinical presentation	60 %	50 %	60 %
Adequately captures severity	56 %	50 %	50 %
Clear and understandable	80 %	60 %	50 %
Follow-up disease manifestation categorisation			
Based on	Disability and function[a,-c]	Progression and remission (long-term impacts)[i,j]	Progression, remission, and impact on daily life[k]
Support (as is or with modifications)	80 %	80 %	60 %
Agree with the general approach	80 %	90 %	60 %
Feasibility to capture data via research studies/secondary data sources	70 %	80 %	60 %
Clear and understandable	70 %	70 %	40 %

[a] van Ettekoven et al. (2019).
[b] Rankin (1957).
[c] Patel et al. (2012).
[d] Dobler et al. (2020).
[e] Bogovic et al. (2014).
[f] Lim et al. (2019).
[g] Barp et al. (2020).
[h] Pustijanac et al. (2023).
[i] Bogovič et al. (2018).
[j] Günther et al. (1997).
[k] Bogovič et al. (2018).

Panellists considered syndromic categorisation the most suitable approach to disease categorisation. Panellists also noted that immunological competence should be considered in specific patient populations and that febrile illness resulting from TBEV infection can be subclassified. Panellists stated that other clinical symptoms, radiological findings, and relevant biomarkers (e.g., elevated neurofilament level in the blood) provide additional insights, further noting duration of symptoms was considered a relatively objective measure whilst memory and concentration dysfunction was more difficult to measure objectively.

3.2.3. Impact on daily life, sequelae, and additional factors to consider regarding classification of the severity of TBEV infection

Table 4 presents panellists' level of agreement on considering various factors in a categorisation system for determining the severity of TBEV infection. There was unanimous agreement ($n = 10$; 100 %) that impact on daily life should be considered in a categorisation system for the severity of TBEV infection. Panellists noted that evaluation of a patient's functional state and their ability to perform activities of daily living reflect clinical severity. Additional points noted in panellists' rationale for agreement included the impact of long-term sequelae—such as frequent headaches and problems with concentration and memory—on daily life and age-related variations in the impact of TBEV infection on daily activities, outcomes, and self-sufficiency. Age was noted as a relevant factor when considering the impact of sequelae related to TBEV infection on daily life (i.e., the impact on daily activities and development or learning outcomes is particularly relevant for children) and dependence on others.

Table 4
Panellist level of agreement on factors to consider in a categorisation system for determining the severity of symptomatic TBEV infection for epidemiological purposes.

Factor	Strongly Agree, %	Slightly Agree, %	Slightly Disagree, %	Strongly Disagree, %	Do Not Know, %
Laboratory results (e.g., liver function, cerebrospinal fluid, serology, RT-PCR testing)	20	50	20	10	NA
Health care resource use (e.g., medical consultations, hospitalisations, laboratory testing, imaging, medications, rehabilitation services)	40	20	30	10	NA
Impact on daily life (e.g., productivity at work or school, dressing, quality of life, feeding, mobility, toileting, bathing, social interactions)	40	60	NA	NA	NA
Sequelae (e.g., fatigue, motor function, cognition/ memory, speech, and learning disorders, seizures)	60	30	NA	10	NA
Outcomes (e.g., admission to the intensive care unit, death)	60	20	NA	10	10

NA = not applicable; RT-PCR = reverse transcription polymerase chain reaction; TBEV = tick-borne encephalitis virus.
Note: Panellists were asked to elaborate further on their level of agreement or disagreement and provide specific examples (e.g., specific laboratory tests and indicative results; specific sequelae and how these would be classified or measured).

There was strong consensus ($n = 9$; 90 %) that sequelae should be considered in a categorisation system for the severity of TBEV infection, as sequelae are measurable, are important for disease severity classification, and impact patients' daily lives. Additionally, the majority of the panellists agreed that outcomes ($n = 8$; 80 %) and laboratory results ($n = 7$; 70 %) should be considered in a categorisation system for the severity of TBEV infection. Panellists reported that key factors that influence outcomes (e.g., ICU admission, mechanical ventilation) may be used as indicators of disease severity, but noted there may be challenges in harmonisation across countries with different healthcare systems. Whilst there are currently limitations in the use of laboratory results to assess disease severity, panellists noted the potential for certain laboratory results (e.g., neurofilament level in blood) to serve as additional criteria for clinical evaluation in the future.

Over half of panellists agreed ($n = 6$; 60 %) that healthcare resource use (e.g., medical consultations, hospitalisations, laboratory testing, imaging, medications, rehabilitation services) should be considered in a categorisation system for TBEV infection, noting that healthcare resource use reflects disease severity especially beyond acute clinical manifestation. Outcomes including time of recovery, prolongation of illness, long-lasting symptoms, and long-term healthcare use due to TBE-related disability (e.g., difficulty walking, limb loss, dependence on a ventilator) were considered relevant indicators of disease severity. However, other panellists considered certain healthcare outcomes, such as length of hospitalisation, to be secondary variables related to severity, and healthcare resources—though relevant—are primarily used for more severe cases.

3.2.4. Considerations for the development of a TBEV infection classification system

For an acute disease manifestation categorisation system, panellists noted alterations of consciousness, focal neurological signs, fever with and without CNS involvement, laboratory values, monophasic or biphasic course, and respiratory insufficiency were additional factors to consider. For a follow-up disease manifestation categorisation system, health-related quality-of-life indicators, disability and functional recovery, and focal neurological signs were noted as factors to be considered by a majority of panellists. Further, when providing recommendations for usability, panellists emphasised the need for clarity in defining fever and the inclusion of clear scoring instructions for physicians, with a special focus on symptom evaluation in younger children. For follow-up, the extraction of all relevant information from medical records was suggested to be the ideal scenario. Furthermore, 3 panellists suggested using questionnaires to gather relevant data, noting that the use of questionnaires may assist with collecting data that are comparable across counties and contributing study centres.

Finally, when asked what factors are of importance for the scientific community in the initial questionnaire, panellists noted the following factors: TBEV subtype categorisation; consideration of vaccination status; assessment of route of infection; patient's functional state after 12 months; clear guidelines and a consensus document; standardised criteria; collaboration between epidemiologists and clinicians; and diagnostic assessments for classification. Panellists acknowledged that some of these factors of importance to the scientific community, such as TBEV subtype categorisation, may not be easily collected at bedside or through patients' medical records.

3.2.5. Remaining areas of uncertainty regarding a standardised TBEV infection categorisation system

Panellists collectively communicated uncertainty with respect to concepts related to separate TBEV infection categorisation systems for adults and children and the ideal timepoint for follow-up after discharge. Results from the initial questionnaire showed that half of the panellists ($n = 5$; 50 %) agreed that there should be a separate disease manifestation system for children, although panellists collectively agreed that comparability was important and that using the same system would be more practical. Additionally, the panellists discussed the differences in disease severity and presentation between young children and adults and did not reach consensus on this topic. In the second questionnaire, a split emerged regarding whether different timepoints for follow-up between children and adults were necessary, with 40 % in agreement, 40 % in disagreement, and 20 % expressing uncertainty.

When generally considering follow-up timepoints, most of the panellists stated that 12 months were appropriate to capture sequelae, health-related quality of life, and disability. However, a few panellists stated that a clinical classification system for follow-up should be captured at multiple timepoints and over a longer time. In the second questionnaire, further exploration of the ideal timepoint for follow-up after discharge revealed a range of preferences, with 30 % advocating for a 6-month follow-up, 20 % supporting a 12-month interval, 30 % suggesting a follow-up exceeding 18 months, and the remaining 20 % favouring alternative options.

When asked how timepoints should be allocated for an ideal categorisation system, panellists described the following timepoints for consideration: at the peak of acute TBEV infection, at hospital discharge, after 6 months to assess outcomes, and long-term follow-up for a comprehensive representation of outcomes and health-related quality of life. Panellists reported that hospital discharge is a standardised timepoint across countries and provides an assessment of acute illness severity at the time of discharge and that preliminary categorisation can be based on the hospital discharge timepoint. Proposed follow-up assessments included outcome assessments (e.g., postencephalitic syndrome severity, quantitative and qualitative assessment of sequelae and health-related quality of life) at 1, 3, 6, and 12 months' post-discharge, and improvement of objective manifestations in the first few years after acute illness.

3.3. Delphi panel: findings from the consensus-building exercise

The 90-minute consensus-building exercise was structured around the outstanding areas of uncertainty following the survey questionnaires. Most topics covered by the first and second survey questionnaires yielded very similar responses from all 10 panellists; these topics were either discussed briefly or were not included in the consensus-building exercise. In areas where consensus was nearly apparent but needed confirming, final confirmation was gathered during the consensus-building exercise.

3.3.1. Overall opinions regarding a clinical classification system for TBEV infection

Prior to discussing the remaining areas of uncertainty, we confirmed panellists' overall opinions regarding a clinical classification system for TBEV infection. All panellists indicated that there is a need for a classification system for TBEV infection and that it is important to have a general standard categorisation system for patients infected with TBEV that optimally reflects both clinical presentation and severity of illness. All panellists ($n = 10$; 100 %) agreed that there are classification systems currently used but expressed concern about their complexity, the lack of standardisation, or the lack of uniform use of these systems. Panellists reported that categorisation of TBEV infection into a disease severity of mild, moderate, and severe based on the presence of meningitis, encephalitis, or myelitis, respectively, is not ideal and a more precise clinical assessment of disease severity is needed. All panellists agreed that a two-part system that separately captures the acute and follow-up phases of TBEV infection is needed. A proposed approach to the development of a classification system for categorisation of disease manifestation of TBEV infection is presented in Fig. 2.

3.3.2. Consensus on classification in the acute phase of symptomatic TBEV infection

Panellists discussed numeric (quantitative), points-based, and clinical measurement approaches for an acute classification system for TBEV infection. Most favoured a combination approach that would be uniform and standardised for comparability purposes. Panellists expressed a need for a system that could be used by any treating clinician, inclusive of general practitioners, neurologists, or infectious disease specialists. Most panellists ($n = 9$; 90 %) indicated that they liked a numerical approach to a classification system due to practicality and ease of use and reiterated the importance of including clinical manifestation and severity. Panellists discussed the Bogovič scale as a good example of an existing numeric scale–based system (Bogovic et al., 2014). Although panellists considered the Bogovič scale an important current approach, they agreed that it is currently too complex for daily practise and therefore needs simplification.

When discussing factors needed in an acute clinical classification system for TBEV infection, panellists agreed that clinical manifestations

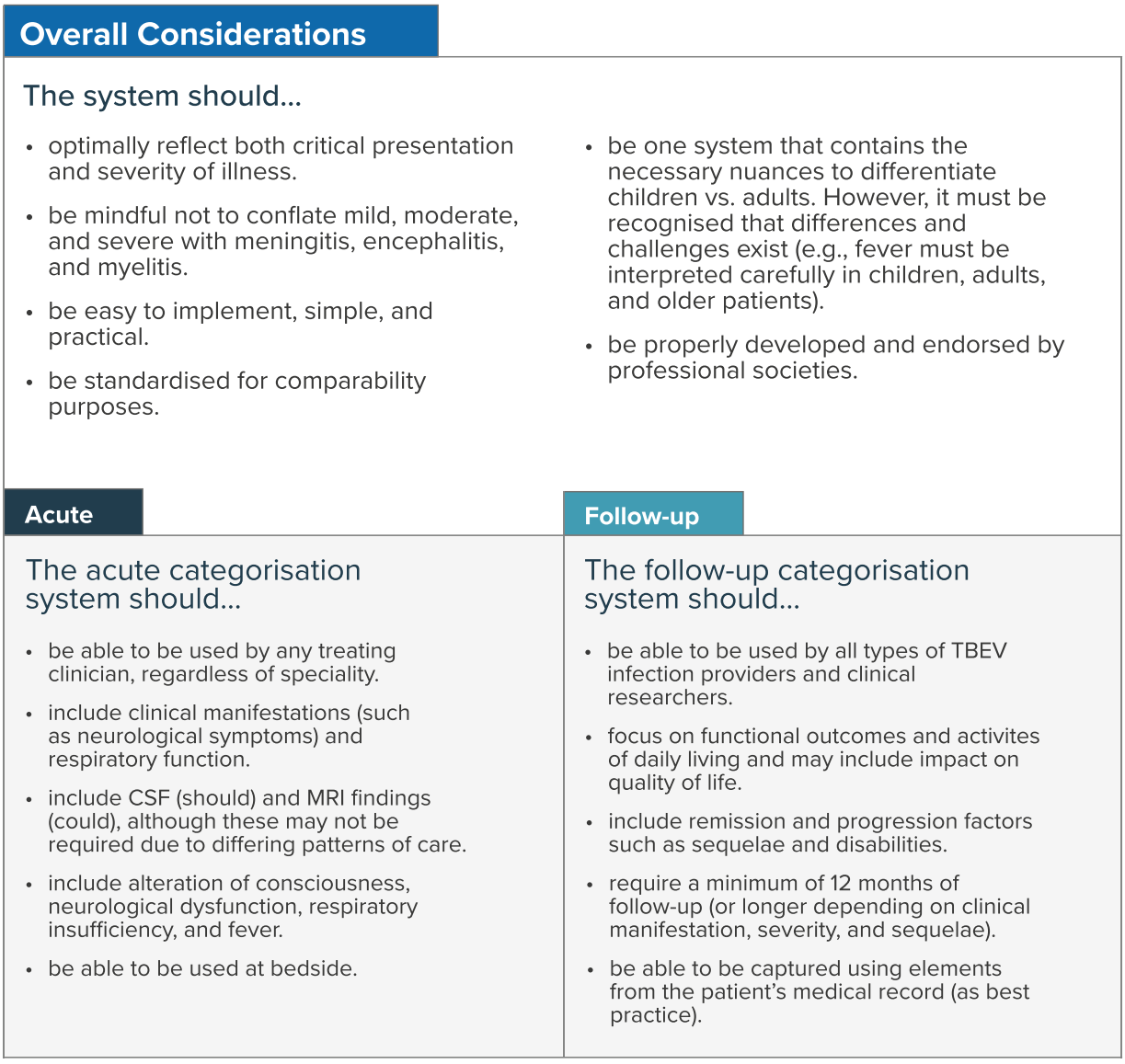

Fig. 2. Proposed approach to the development of a classification system for TBEV infection.
CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; TBEV = tick-borne encephalitis virus

including neurological signs and symptoms, respiration, and cerebrospinal fluid examination should be included in an acute clinical classification system. Panellists further stated that findings from magnetic resonance imaging, which is not performed in every patient, could be included but were not required. Furthermore, panellists noted that fever must be interpreted carefully and did not reach agreement regarding the inclusion of laboratory values and radiological findings.

3.3.3. Consensus on classification in the follow-up phase of TBEV infection

When discussing factors needed in a follow-up clinical classification system for TBEV infection, panellists agreed that health-related quality of life is critical to include. Panellists also agreed that a follow-up system should include factors such as sequelae, disabilities, and subjective and objective symptoms and should describe whether these factors are progressing or whether an improvement can be observed. Most panellists agreed ($n = 9$; 90 %) that a follow-up clinical classification system should consist of elements that are included in a patient's medical records. The panellists discussed the challenges that may arise with this approach due to differences across countries and facilities, with one panellist recommending being inclusive of low- and middle-income countries whilst also taking a pragmatic approach.

3.3.4. Considerations on a separate disease manifestation system for children

Panellists discussed whether careful wording could be included in one system that is sufficiently nuanced for children and adults but did not achieve consensus on this topic. Panellists agreed that one system would be ideal, as it would be more practical and facilitate comparability across studies; however, they discussed difficulties detecting certain symptoms (e.g., neck stiffness) in younger children and challenges such as determining age categories. For example, although disease presentation may differ between adult and paediatric populations, panellists noted that a 17-year-old patient may manifest the same as an adult, and there may be nuances around manifestation in older or comorbid patients.

3.3.5. Timepoints for follow-up

Panellists discussed the ideal timepoint for follow-up after discharge for disease manifestation categorisation for TBEV infection and arrived at agreement on a 12-month follow-up post-discharge, but also noted that additional follow-up timepoints may be beneficial. Several panellists desired follow-up at multiple timepoints (e.g., 3 months, 12 months, 3 years) as a function of the severity and duration of the sequelae.

Panellists noted that follow-up assessments at specific intervals allow for monitoring outcomes and the evolution of postencephalitic symptoms, and long-term follow-up is necessary for a comprehensive understanding of outcomes and health-related quality of life.

4. Discussion

The findings of this Delphi panel exercise underscore the need for a feasible and practical classification system for TBEV infection. Panellists agreed that it is important to have a general standard categorisation system for patients infected with TBEV that optimally reflects both the clinical presentation and severity of illness of such patients, noting that a critical gap persists in the absence of a classification system that effectively captures both these aspects of TBEV infection. Specifically, there is a need for a two-part classification system that separately captures the acute and follow-up phases of symptomatic TBEV infection. Furthermore, this system should be clinically oriented and include an overall score with ranges depicting the severity of TBEV infection.

Whilst there are existing systems used for the categorisation of disease manifestation, a comprehensive system is currently lacking. Ideally, such a system should capture both the acute and follow-up phases of TBEV infection, be feasible for use at bedside, be clear and easy to understand, and adequately capture both clinical presentation and severity. The clinical manifestations of acute TBEV infection are well established, and panellists in this Delphi exercise described several factors that should be considered when classifying the acute phase of the disease, including alterations of consciousness, respiratory insufficiency, and presence of clinical and radiological nervous system involvement. For a follow-up disease manifestation categorisation, panellists noted that health-related quality-of-life indicators, disability, and functional recovery should be considered. To assess the patient's functional status, the panellists suggested various scales that may be used, such as the modified Rankin Scale, the Karnofsky Performance Status Scale, and the EQ-5D-Y (Mor et al., 1984; Quinn et al., 2009; Ravens-Sieberer et al., 2010). One panellist noted that there is currently no validated measure appropriate for encephalitis and that encephalitis-specific measures are being developed (Tooren et al., 2022). Finally, panellists noted that long-term follow-up is necessary for a comprehensive understanding of outcomes and health-related quality of life, and multiple follow-up timepoints may be needed depending on disease severity and the duration of sequelae. In alignment with this recommendation, a study assessing self-reported sequelae of surveillance-reported TBE cases in Germany found that half of the adult cases and 5 % of the paediatric cases reported persisting sequelae 18 months after symptom onset (Nygren et al., 2023b), underscoring the need for long-term follow-up.

Overall, the results of our Delphi panel highlighted the need for careful consideration of disease manifestation in adults versus children, as well as a particular focus on symptom evaluation in young children. For instance, panellists noted that certain sequelae, such as learning disabilities, may be particularly difficult to assess or diagnose in children. Indeed, several studies have reported differences in disease manifestation between children and adults in Europe (Krawczuk et al., 2020; Logar et al., 2000, 2006; Nygren et al., 2023a). For example, in a prospective cohort study of TBE cases in Germany, Nygren et al. (2023a) found that fever was more common in children, whilst myalgia was more common in adults. Additionally, in a retrospective analysis of TBE cases in Poland, Krawczuk et al. (2020) reported that nausea and vomiting were more frequent in children, whereas neurological manifestations were more frequent in adults. The authors additionally found that motor sequelae were less frequent in children than adults (Krawczuk et al., 2020). Other European studies infrequently reported meningoencephalitis and rarely reported meningoencephalomyelitis in paediatric populations (Parfut et al., 2023; Steffen, 2019). Furthermore, the classic biphasic TBE disease course often seen in adults has been inconsistently reported in children, further emphasising a need for tailored categorisation systems for adult and paediatric patients (Parfut et al., 2023; Steffen, 2019). Logar et al. (2006) also reported that senior adults (aged over 60 years) reported more fatigue, altered consciousness, and decreased muscle strength during the second phase of TBE than adults (under 60 years), highlighting another potential nuance to consider when developing a classification system.

This Delphi exercise focused on characterising CNS symptoms of TBEV infection in alignment with the ECDC TBE case definition. The categorisation system should be expected to apply to all TBEV subtypes, thereby allowing differences in presentation/severity to be compared. The system should be developed with the clinical presentation of all subtypes in mind, not only the European subtype. In addition, nervous system presentations of TBEV infection are known to include peripheral and autonomic presentations as well as those of CNS (Du Four et al., 2018; Neumann et al., 2016). There may be value in the ECDC criteria broadening their definition of TBE, and in the community of clinicians, researchers, and other TBE specialists considering all aspects of nervous system involvement, when aligning on a categorisation system. Additionally, whilst not discussed during the Delphi panel exercise, neurophysiological assessment and changes to patients' social history and professional life after TBEV infections should be included in a future categorisation system. This panel exercise provides the precursory findings to support the next steps for implementing a new classification system, which include assessing reliability, validity, and ease of use in clinical settings, whilst considering feasibility of use across different regional practice patterns.

The findings of this study are subject to the limitations inherent to Delphi panel exercises. Whilst efforts were made to identify and include thought leaders from a broad geography to obtain inputs from multiple countries, panellists' responses reflect their experiences with unique patient populations and thus diversity of thought regarding clinical categorisation and severity thresholds. Although clinical courses and outcomes vary among infections with different TBEV subtypes, the subtypes can cause similar debilitating neurological symptoms and sequelae, ranging in degree of severity (European Centre for Disease Prevention and Control, 2024). Current categorization and clinical classification systems for TBEV infection lack consistency, and the results of this panel exercise are intended to be applicable across TBEV subtypes. We acknowledge that the panellists were limited to experts within Europe, where the European TBEV subtype is predominant; however, other subtypes have been reported to co-circulate in these regions (Amicizia et al., 2013; Jääskeläinen et al., 2006; Lundkvist et al., 2002). The insights of this panel may not reflect those of TBEV experts from non-European countries or the nuances associated with other TBEV subtype infections. Future development of this work should include individuals from non-European countries with expertise across all major subtypes. The sample size of 10 panellists may not reflect all countries and medical specialities, and full generalisability cannot be expected; however, this is a common and manageable sample size for Delphi panels, which often range from 8 to 20 panellists (Beiderbeck et al., 2021; Shang, 2023). In addition, although panellists' cameras were turned off during the consensus-building exercise, it is possible that panellists may have been able to recognise the voices of others participating, thereby limiting the ability to achieve full blinding. Finally, all the invited panellists agreed to participate in this research; these panellists may not reflect the full community of TBEV infection experts, and the opinions of those who agreed to participate may be systematically different from those who did not agree to participate. The study team was unable to measure or control for this potential bias. However, panellists included practising clinicians treating TBEV infection, a non-governmental organisation representative, and an epidemiologist with expertise in infectious diseases and a high familiarity with the condition. Given the relatively small community of clinicians who are experts in TBEV infection, it is unlikely that opinions would vary greatly throughout the clinical community of those who diagnose, follow, and treat the condition. Moreover, this well-chosen sample of panellists who are keenly aware of treatment modalities and challenges within TBEV

infection classification provided actionable insights that may inform the development of standardised disease manifestation categories in patients infected with TBEV.

5. Conclusions

This Delphi panel study found that a critical gap persists in the absence of a feasible and practical classification system for TBEV infection. The need for a clinical classification system for symptomatic TBEV infection is heightened due to the increasing challenge posed by TBE and the need to enhance patient outcomes. Our findings gleaned from the expert panellists underscore the need for further research aimed at developing a user-friendly classification system that captures the acute and follow-up (outcome) phases of symptomatic TBEV infection and optimally reflects both clinical presentation and severity of illness. Additionally, the results of our Delphi panel highlighted the need for careful consideration of disease manifestation in adults versus children, with emphasis on sequelae, outcomes, and impacts on quality of life. These findings may be used to inform the development of a clinical classification system for TBEV infection, which will enhance patient care and foster comparability among studies, thereby supporting treatment development, refining vaccine strategies, and fortifying public health surveillance and preparedness.

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Role of the sponsor

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CRediT authorship contribution statement

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Declaration of competing interest

J.R. and M.P. are full-time employees of RTI Health Solutions, an independent nonprofit research organisation, which received funding from Pfizer in connection with the development of this manuscript. Their compensation is unconnected to the studies on which they work. M.G. was a full-time employee of RTI Health Solutions at the time this study was conducted. K.H., H.M., F.J.A., and A.P. are employees of Pfizer Inc. and hold stock and stock options in Pfizer Inc. W.E. was an employee of Pfizer Inc. at the time of the project, and holds stock options in Pfizer Inc. A.E. does not receive any personal grants or honoraria from corporate or pharmaceutical companies. Encephalitis International (of whom A.E. is Chief Executive) does receive grants, expenses, and honoraria from a range of corporate partners, including the sponsor of this study (Pfizer) and other pharmaceutical companies involved in tick-borne encephalitis. J.S. received consulting fees from Pfizer. F.S. served on the scientific advisory board on Lyme disease serological diagnostics for Roche, served on the scientific advisory board on Lyme disease and panel on TBE for Pfizer, and is an unpaid member of the steering committee of the ESCMID Study Group on Lyme Borreliosis/ESGBOR. M.V. has received consultancy funding from Bavarian Nordic and Pfizer Vaccines. D.Z. declares a research grant within the Research Collaboration to Rīga Stradiņš University (employer) from Pfizer Vaccines. U.K.M.-L has received consulting and lecture fees from Pfizer and Biogen. G.D., G.K., L.K., J.K., and J.Z. have no conflicts of interest to disclose.

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Data availability

Survey data will be made available upon request to Pfizer; transcript data cannot be shared to protect participant anonymity.

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