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Original article

Incidence, healthcare resource utilization and costs of hospitalized patients with tick-borne encephalitis (TBE) in Italy

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ABSTRACT

Objective: Our study's objective was to assess the incidence trends and healthcare resource utilization of hospitalizations for Tick-Borne Encephalitis (TBE) and associated costs in Italy in order to improve public awareness and preventive measures.

Methods: This retrospective observational study was based on the Italian Ministry of Health's Hospital Discharge Record (HDR) database. Data were gathered across Italy from 2015 to 2019, selecting hospitalizations with ICD-9 code 063 related to TBE, both in primary and secondary diagnoses. For each year, we collected the following variables: number of hospitalizations, hospitalization rate, mortality rate, mean length of hospital stay, hospital ward, and cost of hospitalization.

Results: There were a total of 237 hospitalizations from 2015 to 2019; 62 % of those were male. The lowest number of TBE hospitalizations was in 2015 (21 cases, corresponding to 0.35 per million inhabitants), the highest in 2019 (64 cases, 1.04 per million inhabitants). The summer months saw a greater than average number of hospitalizations. For the years analyzed, the cumulative number of cases peaked in June (54 cases), July (46 cases), and August (35 cases). There were only two deaths registered in our study sample. TBE cases were mostly localized in the North-Eastern regions of Italy. TBE incidence during the study period in the most affected areas were: Autonomous Province of Trento, ranging from 11.2 to 42.3 per million inhabitants, Autonomous Province of South Tyrol, from 0 to 21.1 per million inhabitants, and Veneto Region, from 2.6 to 4.5 per million inhabitants. In the study period, the average length of hospital stay was largely stable ranging from 10.6 days to 12.8 days, with related costs ranging from 5,813.7 € to 7,352.5 €.

Conclusions: According to our data, the majority of TBE hospitalizations occur in North-East Italy with an increasing trend over the analyzed period. Even though Italy has fewer TBE cases than other neighboring European countries, the health and economic impact can be high in the affected areas.

1. Introduction

Numerous microorganisms can cause meningitis, encephalitis, and meningoencephalitis, but viral aetiologies are the most common (Granerod et al., 2010). The three viruses most frequently linked to encephalitis, meningoencephalitis, and meningitis in both pediatric and adult populations are enterovirus (EV), herpes simplex types 1 and 2 (HSV-1 and HSV-2), and varicella zoster virus (VZV) (Bartt, 2012).

A second group of vector-transmitted encephalitic viruses (referred to as flaviviruses) can also target Central Nervous System (CNS) neurons and cause cytopathology (Kohil et al., 2021). Tick-borne encephalitis (TBE) is an acute infection of the central nervous system, caused by

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Tick-borne encephalitis virus (TBEV), which is usually transmitted to humans by a tick bite (*Ixodes ricinus* or *Ixodes persulcatus*) (Riccò, 2021). The three main subtypes of the tick-borne encephalitis virus (TBEV) are called European (TBEV-Eu), which is prevalent in Italy and other Central European countries, Siberian (TBEV-Sib), and Far Eastern (TBEV-FE). They differ in terms of their vector competence, geographic distribution across Europe and Asia, and human severity (Ecker et al., 1999).

Following infection with the TBEV, there is a noticeable immune cell infiltration composed of lymphocytes and macrophages in the brain stem, cerebellum, and cortex (Lindquist and Vapalahti, 2008). Inflammation can arise in distinct anatomical regions such as the meninges (meningitis), brain (encephalitis), and spinal cord (myelitis), or simultaneously in multiple regions (meningoencephalitis, encephalomyelitis) (Kohil et al., 2021).

The clinical manifestations of TBE in symptomatic subjects follow a biphasic course with fever and influenza-like symptoms during a brief first phase. In around 20 %−30 % of cases, neurological disorders of varying severity (meningitis, meningoencephalitis, meningoencephalomyelitis) occur in a second phase of the disease. The two phases are separated by an asymptomatic period of 1–33 days (Haglund and Gunther, 2003). In some patients, TBE can have prolonged periods of activity in the CNS, which keeps the infectious process ongoing. In this situation, TBE develops into a chronic progressive illness (Ruzek et al., 2019).

In the first phase, TBEV can be detected in blood samples by RT-PCR, while patients during the neurological phase are diagnosed through serological identification for TBE-specific IgG and IgM or cerebral spinal fluid analysis for TBE IgM (Ergunay et al., 2016).

Given that there is no specific treatment, paracetamol and non-steroidal anti-inflammatory drugs, including metamizol, are administered for pain and fever management during the acute neurologic phase. Brain stem involvement can cause difficulties in swallowing, respiratory insufficiencies and seizures. Severe cases may need treatment in intensive care settings (Ruzek et al., 2019).

According to the World Health Organization, vaccination is considered the most effective prevention measure for TBE (WHO Publication, 2011). Two TBE vaccines are currently on the market in Europe: Encepur® (Bavarian Nordic) and FSME-IMMUN®/TICOVAC® (Pfizer). In Italy, only the latter one is available (Panatto et al., 2022).

Italy is often considered a country at low risk for TBE, however, the North-East regions, corresponding to pre-alpine and alpine areas called “Triveneto” including Trentino-Alto Adige, Veneto and Friuli Venezia Giulia regions are particularly affected by this infection (Rezza et al., 2015). In particular, the province of Belluno (Veneto), is classified by the World Health Organization (WHO) as a highly endemic area (i.e. the WHO defines highly endemic areas as those with a yearly incidence >5 cases per 100,000 population), with an annual average incidence of 5.95 cases per 100,000 population between 2007 and 2018 (Cocchio et al., 2020). In the other North-Eastern regions, the annual incidence of TBE is 0.48 per 100,000 population for Veneto in the period 2007–2018 (Cocchio et al., 2020), and 0.1–1.0 per 100,000 population for Friuli Venezia Giulia in the period 2000–2013 (Rezza et al., 2015). However, a recent study in Germany has shown that patients with typical TBE symptoms are likely under-tested which is potentially leading to under-ascertainment of TBE infections (Schley et al., 2023). In this context, the aim of our study was to evaluate trends and characteristics of TBE hospitalizations in Italy to increase public understanding and to guide prevention policies.

2. Methods

This is a retrospective observational study based on the Italian Ministry of Health’s Hospital Discharge Record (HDR) database, reported in accordance with the RECORD (The REporting of studies Conducted using Observational Routinely-collected health Data) statement (Benchimol et al., 2015). Because only anonymized data were used, neither ethical approval nor informed consent from patients were required for this study. HDRs routinely collect demographic and clinical data on all patients admitted to Italian public and private hospitals.

Each HDR, coded by ICD-9-CM coding system (International Classification of Disease, 9th Revision, Clinical Modification), reports primary and secondary diagnoses, together with surgical interventions, diagnostic and therapeutic procedures performed during hospitalization.

Data were collected from 2015 to 2019 across Italy, considering patients of all genders and age groups.

Analyzing the existing literature, we selected the following ICD-9 code related to Tick-borne viral encephalitis (063), both in primary and secondary diagnoses:

- 063.0 Russian spring-summer [taiga] encephalitis
- 063.1 Louping ill
- 063.2 Central European encephalitis
- 063.8 Other specified tick-borne viral encephalitis
- 063.9 Tick-borne viral encephalitis, unspecified

Outcome measures included the number of hospitalizations, hospitalization rate, mortality rate, mean length of hospital stay, hospital ward, and cost of hospitalization based on Diagnosis Related Groups (DRG). The reimbursement system based on DRGs does not provide real costs, but an estimate of the costs related to hospitalization, classifying patients into homogeneous classes (DRG codes) based on the ICD-9 diagnostic codes assigned at the time of discharge, age, sex, and consumption of healthcare resources.

Outcomes were reported for Italy as well as stratified by region, including those with known high incidence of TBE and existing local clusters.

3. Statistical analysis

We reported descriptive and analytic statistics. Discrete data were reported as numbers and percentages, while continuous data as means and standard deviations with a 95 % confidence interval (CI). The hospitalization rate was calculated as the number of hospital admissions per year divided by the resident population in the same period, as reported by the Italian National Statistics Institute (Italian National Statistics Institute ISTAT, 2023). We calculated the cost of hospitalizations through the rates of the Italian national cost nomenclator (DRG) (Ministero della Salute, 2012). For data analysis, we used Microsoft Excel 2016 (Microsoft Corporation, 2016) and STATA 13 (StataCorp, 2013) software.

4. Results

During the study period (2015–2019) there were 237 hospitalizations (an average of 47.4 hospitalizations per year) including all age groups. Overall, 62 % of hospitalized persons were males. The incidence was highest in the 55–74 year-olds (34.2 % of all hospitalizations) and 35–54 year-olds (27.8 % of all hospitalizations), followed by the age group of 15–34 (16.5 % of all hospitalizations), while the elderly (>75 years) and infants and children (0–14 years) were less affected (13.5 % and 8.0 % of all hospitalizations, respectively) (see details in Supplementary Figure 1).

As shown in Fig. 1, the number of hospitalizations increased from 2015 to 2016, remained stable until 2018 and then increased again in 2019.

Fig. 2 shows the cumulative number of cases by month. A clear seasonal pattern is visible with a higher number of cases recorded from May to November, with an evident peak during summer season.

The number of hospitalizations based on type of diagnosis is reported in Table 1. TBE-specific codes were rarely assigned in secondary position, except for 2019 (16% vs 4–11 % in the previous years).

According to regional analysis of hospitalization rate (Fig. 3), the TBE cluster was localized in the North-eastern regions, in particular in

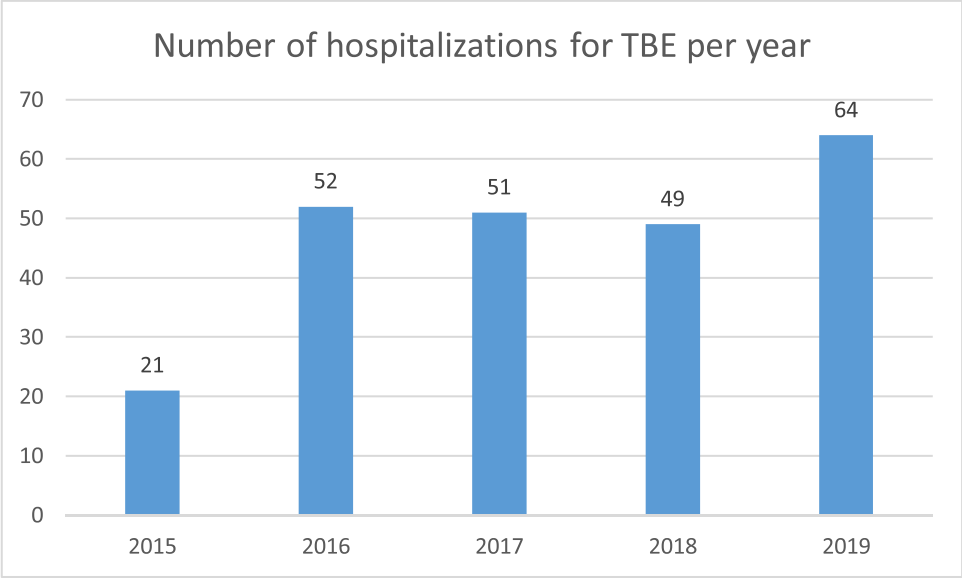


Fig. 1. Number of hospitalizations for TBE per year.

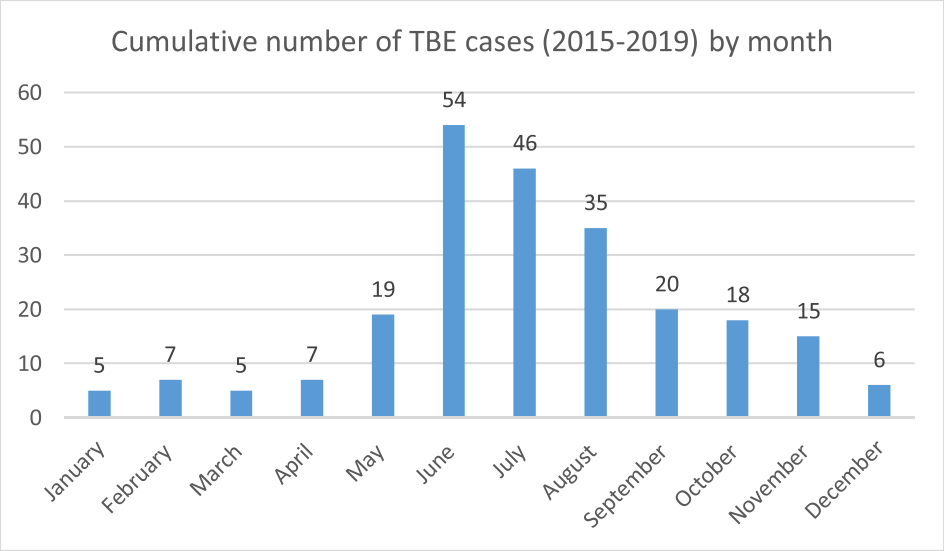


Fig. 2. Cumulative number of TBE cases (2015–2019) by month.

Table 1
Number of hospitalizations for TBE sorted by type of diagnosis.

	2015	2016	2017	2018	2019	Total
Primary diagnosis	19	49	48	47	54	217
Secondary diagnosis	2	3	3	2	10	20
Total	21	52	51	49	64	237

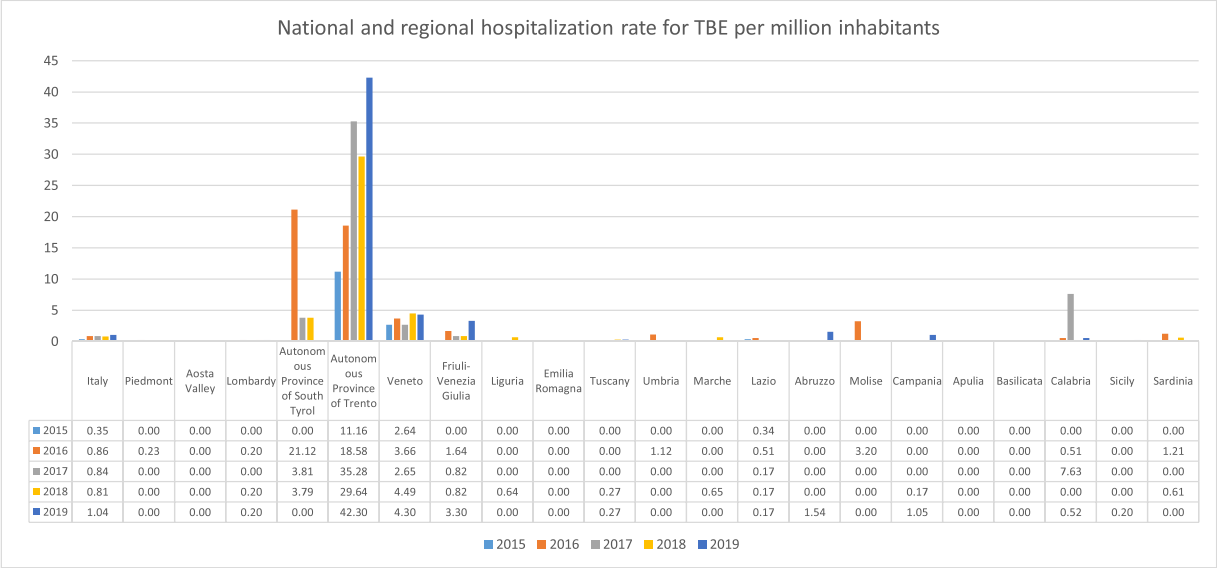
the regions of "Triveneto" (the Autonomous Provinces of Trento and South Tyrol, Veneto and Friuli Venezia Giulia). The highest hospitalization rate was registered in Autonomous Provinces of Trento, ranging from 11.16 per million inhabitants in 2015 to 42.30 per million inhabitants in 2019.

The mean length of hospital stay for TBE in Italy was mostly stable in the considered period, with a maximum of 12.8 days in 2015 and a minimum of 10.6 days in 2017. Out of 237 hospitalizations, the majority of patients (84.8 %) left the hospital as routine discharge, while 5.5 % of patients were referred to other institutions for acute care. The most common hospital wards were: Infectious and Tropical Diseases (37.5 %), General Medicine (27.0 %), and Neurology (12.2 %). Only 2 deaths (Case Fatality Rate 0.8 %) occurred in the five years considered, both in 2019.

We did not find substantial differences among mean costs of hospitalization during the study period (Table 2). Eighty-five percent of hospitalized patients were associated with DRG code 561 "Non-bacterial infection of nervous system except viral meningitis". For the entire period, the national cumulative cost of TBE burden for all years, in terms of DRG, was 1627,194 Euro, with the Veneto region being the most impacted (Table 3). The average costs varied greatly, from € 4420 (Tuscany) to € 34,546 (Molise), due to different length of stay and co-morbidity or complications for each patient.

5. Discussion

Our results show that TBE is a rare disease in Italy, with an average number of 47 hospitalized cases per year between 2015 and 2019, which



	Italy	Piedmont	Aosta Valley	Lombardy	Autonomous Province of South Tyrol	Autonomous Province of Trento	Veneto	Friuli-Venezia Giulia	Liguria	Emilia Romagna	Tuscany	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Apulia	Basilicata	Calabria	Sicily	Sardinia
2015	0.35	0.00	0.00	0.00	0.00	11.16	2.64	0.00	0.00	0.00	0.00	0.00	0.00	0.34	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2016	0.86	0.23	0.00	0.20	21.12	18.58	3.66	1.64	0.00	0.00	0.00	1.12	0.00	0.51	0.00	3.20	0.00	0.00	0.00	0.51	0.00	1.21
2017	0.84	0.00	0.00	0.00	3.81	35.28	2.65	0.82	0.00	0.00	0.00	0.00	0.00	0.17	0.00	0.00	0.00	0.00	0.00	7.63	0.00	0.00
2018	0.81	0.00	0.00	0.20	3.79	29.64	4.49	0.82	0.64	0.00	0.27	0.00	0.65	0.17	0.00	0.00	0.17	0.00	0.00	0.00	0.00	0.61
2019	1.04	0.00	0.00	0.20	0.00	42.30	4.30	3.30	0.00	0.00	0.27	0.00	0.00	0.17	1.54	0.00	1.05	0.00	0.00	0.52	0.20	0.00

Fig. 3. National and regional hospitalization rate for TBE per million inhabitants.

Table 2
Hospitalization length for TBE and related costs.

	2015	2016	2017	2018	2019
Mean hospital stay (days)	12.8	12.3	10.6	10.7	11.0
Mean cost per hospitalisation	5813.7 €	7352.5 €	7339.4 €	6673.7 €	6137.7 €

Table 3
National and regional cost analysis for TBE hospitalizations.

	N. of TBE cases	Total cost (€)	Average cost per case
Italy	237	1627,194	6865.8
Piedmont	2	40,604	20,302.0
Aosta Valley	0	0	0
Lombardy	3	46,662	15,554.0
Autonomous Province of South Tyrol	17	131,474	7733.8
Autonomous Province of Trento	72	463,469	6437.1
Veneto	91	582,301	6398.9
Friuli Venezia Giulia	9	50,606	5622.9
Liguria	0	0	0
Emilia Romagna	0	0	0
Tuscany	2	8840	4420.0
Umbria	1	6058	6058.0
Marche	1	6058	6058.0
Lazio	8	39,327	4915.9
Abruzzo	2	9110	4555.0
Molise	1	34,546	34,546.0
Campania	7	33,493	4784.7
Apulia	0	0	0
Basilicata	0	0	0
Calabria	17	150,414	8847.9
Sicily	1	6058	6058.0
Sardinia	3	18,174	6058.0

corresponds to an average annual incidence of 0.8 hospitalized cases per million inhabitants. However, the regional hospitalization rate stratified by region highlights that TBE is mainly localized in a small geographical area in the North-East of Italy, where the reported rate of TBE infections reaches the endemicity definition by WHO. Hospitalizations occurred more frequently during the summer period, which is likely to be due to increased tick activity in warmer weather as well as more people pursuing outdoor activities in that period. Regarding the geographical distribution of TBE cases, Rezza et al. (Rezza et al., 2015) reported a great variability of incidence within the same region or the same province. For instance, the municipality of Tramonti di Sopra, province of Pordenone, registered a mean annual incidence rate of 181.2 per 100,000 inhabitants between 2000 and 2013 vs 0.4 per 100,000 inhabitants registered in the whole province of Pordenone during the same period.

Comparing our work with other existing Italian epidemiological studies, we found similar results regarding the Veneto region reported by Cocchio et al. (Cocchio et al., 2020) during 2007–2018. In the Veneto Region, we found an average of 18 cases per year vs 16 cases per year identified by Cocchio et al.; both studies were based on HDRs. Two studies identified TBE cases from infectious diseases units and public health districts. Rezza et al. (Rezza et al., 2015) reported 26 mean cases per year from 2000 to 2013 in the Triveneto region compared to 38 mean cases per year of our study, while Alfano et al. (Alfano et al., 2020) reported 6 mean cases per year from 1992 to 2019 in the Autonomous Province of Trento compared to 14 mean cases per year of our study. The annual reports from Italian National Health Institute (Istituto Superiore di Sanità, or ISS) (Istituto Superiore di Sanità, 2023) reported 39 cases of TBE in Italy in 2018 (−20 % compared to our study), and 24 cases in 2019 (−63 % compared to our study). ISS bulletins rely on the Arbovirus Surveillance System, which gathers data from regional Infectious Disease Centers. As outlined by Cocchio et al. (Cocchio et al., 2020), it's worth noting that these data only partially overlap with HDRs.

Riccò (Riccò, 2021) in his letter also used ISS data, from 2017 to 2020, reporting 26 mean cases per year in Italy (−45 % as opposed to our work). Those differences could be due to different periods or data sources. We also checked ISS reports from the following years and found that the overall number of TBE cases increased (40 cases in 2022 and 50 cases in 2023), with a higher incidence of cases in Friuli Venezia Giulia and Emilia Romagna, a region previously spared from TBE.

Italy has fewer registered TBE cases than other European countries. Considering bordering countries, the TBE Book (5th Edition) (Dobler et al., 2022) reported for 2022 an incidence of 29 cases (SD 11) per million inhabitants in Switzerland, 12 cases (SD 4) per million inhabitants in Austria, 49 cases (SD 16) per million inhabitants in Slovenia, while France reported a lower incidence, with 0.3 cases (SD 0.1) per million inhabitants. The most endemic European countries are Lithuania (179 cases per million inhabitants, SD 58), Latvia (91 cases per million inhabitants, SD 19), Czech Republic (58 cases per million inhabitants, SD 15), while Russia has the highest number of cases per year,

but a lower incidence (14 cases per million inhabitants, SD 2).

Even if the number of reported Italian cases is low, for the study period we estimated a mean cost for the Italian Healthcare System of € 325,439 per year, with a peak of € 421,461 in 2019. Moreover, as this cost has been estimated based on DRGs, it does not include costs related to the management of long-term neurological and psychological sequelae that significantly impact the affected individuals' quality of life, such as persistent headache, weakening or loss of hearing, ataxia, depression, anxiety (Pustijanac et al., 2023). As for costs related to TBE treatment and its sequelae, Mihajlović et al. in their study aimed to assess the cost-effectiveness of a potential anti-tick vaccine that would protect against both Lyme borreliosis and TBE in Slovenia (Mihajlovic et al., 2019), they reported the following as direct medical costs for TBE: cost of treating meningitis € 1235, moderately severe meningoencephalitis € 2915, severe meningoencephalitis and meningoencephalomyelitis € 11,100, intensive care unit € 20,400, meningitis sequelae € 70, moderately severe meningoencephalitis sequelae € 122, severe meningoencephalitis and meningoencephalomyelitis sequelae € 28,592; as for indirect costs, an average of 48 days of work absence was estimated. On the other hand, the costs associated with vaccination campaigns must also be considered. In Italy, the public price of a single dose of TBE vaccine (TICOVAC®) varies from 70 € for the children's formulation to 81 € for the adult's formulation (Farmadati Italia, 2024). Therefore, a complete primary vaccination cycle, consisting of three primary doses, amounts to an overall cost of 210–243 € per person.

While offering new and important insights into the hospitalization of TBE cases in Italy, the study may have underestimated the real incidence of TBE, for three reasons. First, we considered only HDR, as opposed to Cocchio et al. (Cocchio et al., 2020) who analyzed also the mandatory notification system (MNS) through record-linkage. Secondly, our data encompassed only hospitalized patients, eventually missing persons affected by TBE with mild symptoms. Thirdly, we cannot exclude the probability that some TBE patients were not diagnosed or were miscoded by applying an unspecific code for encephalitis, myelitis, meningitis and encephalomyelitis.

Another factor we took into consideration is the scarce awareness of diseases spread by arthropods, and tick-bites in particular, among workers and tourists. As pointed out by Riccò et al. (Riccò et al., 2020), 43 % of farmers interviewed in the endemic area knew about the TBE vaccine, 25 % of them were vaccinated, while only 54 % applied protective habits. Regarding tourists in the Dolomites area, Riccò et al. (Riccò et al., 2023) reported a low incidence of TBE vaccine (24 %) and knowledge of TBE occurrence in this area (52 %).

Due to its potentially severe clinical course, lack of specific pharmacological treatment, and possible long-term consequences, prevention strategies should be improved, as recommended by the Italian National Vaccination and Prevention Plan for 2017–2019 (G.U. Serie Generale n. 41, 2017), for residents of endemic areas and also for workers of rural and mountain areas. Preventive strategies could be:

- increase the vaccination coverage in the endemic areas, providing free vaccines to all residents and workers in endemic areas as already implemented in Autonomous Province of South Tyrol, Autonomous Province of Trento, Friuli Venezia Giulia Region, and Belluno Province;
- promote communication campaigns aimed at tourists and workers to avoid tick bites in the first place (avoidance of interested areas, use of repellents and clothes with long sleeves and pants), checks and prompt removal of ticks and/or to get the TBE vaccine 9–12 months in advance before traveling to endemic areas;
- raise awareness among general practitioners, pediatricians and occupational physicians working in endemic areas about TBE risk, recommending the vaccine to exposed population.

6. Conclusions

According to our data, the majority of TBE hospitalizations occur in North-East Italy with an increase trend over the analyzed period. Even though Italy has fewer TBE cases than other neighboring European countries, the health and economic impact can be high in the affected areas.

CRediT authorship contribution statement

Renzo Scaggiante: Writing – review & editing, Formal analysis. **Liliana Guadagni:** Writing – original draft, Methodology, Formal analysis. **Massimiliano Orso:** Writing – original draft, Methodology, Formal analysis. **Daniela d'Angela:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Funding acquisition. **Ciro Carrieri:** Writing – review & editing, Investigation, Formal analysis. **Barbara Polistena:** Writing – review & editing, Formal analysis. **Federico Spandonaro:** Writing – review & editing, Formal analysis. **Ilaria Bertoldi:** Writing – review & editing. **Andreas Pilz:** Writing – review & editing, Formal analysis, Conceptualization. **Katharina Schley:** Writing – review & editing, Formal analysis, Conceptualization. **Raffaella Iantomasi:** Writing – original draft, Formal analysis, Conceptualization.

Competing interests

RS was paid consultant to Pfizer in connection with the development of this manuscript. RI, IB, KS and AP are employees of Pfizer and may hold Pfizer stocks or stock options. CC, DA, LG, MO, BP, and FS are employees of C.R.E.A. Sanità, which received funding from Pfizer in connection with the development of this manuscript.

Data availability

All data supporting the findings of this study are available within the paper and its supporting file.

Declarations

Ethics approval and consent to participate

Ethical approval and patients' informed consent for this study were not required because only anonymized data were used.

Consent for publication

Not applicable.

Availability of data and materials

All data supporting the findings of this study are available within the paper and its supporting file.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ttbdis.2024.102372.

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