

TBE in Italy

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E-CDC risk status: endemic (data as of October 31, 2022)

History and current situation

Italy is considered a low-incidence country for tick-borne encephalitis (TBE) in Europe.¹ Areas at higher risk for TBE in Italy are geographically clustered in the forested and mountainous regions and provinces in the northeast part of the country, as suggested by TBE case series published over the last decade.²⁻⁵ A national enhanced surveillance system for TBE has been established since 2017.⁶ Before this, information on the occurrence of TBE cases at the national level in Italy was lacking. Both incidence rates and the geographical distribution of the disease were mostly inferred from endemic areas where surveillance was already in place, ad hoc studies and international literature.¹

TBE has been recorded in Italy since 1967, with foci of infection in the northeast (Trento, Belluno and Gorizia) and central (Florence and Latina) provinces.⁷⁻¹⁰ TBE presence in central Italy has not been confirmed by further studies on ticks and serosurveys conducted afterwards,¹¹⁻¹² nor by human cases, suggesting the disappearance of these small endemic foci.

Serological investigations of people at risk, such as forestry rangers, hunters, and mushrooms collectors, have been performed in order to get information on the TBE virus (TBEV). Circulation in the pre-alpine and alpine regions reporting seroprevalence values of 0.6%, 1.07% and 3.2% in Friuli-Venezia Giulia,¹³ Trento province¹⁴ and Turin province,¹⁵ respectively. Interestingly, Turin province has never reported human cases of TBEV infection, so far.

A retrospective study conducted in 2015 in the northeast regions, allowed the identification of 367 cases (0.38 per 100,000 inhabitants) during the period from 2000 to 2013.³ TBE cases were mainly males (70%), and around 70% of them were between 30 and 70 years of age. A significant increase in the annual incidence rate (IR) was observed during the study period, from 0.18 per 100,000 in the year 2000 up to 0.59 per 100,000 in 2013 (incidence rate ratio [IRR]=1.05 per 1 calendar year increase, 95% confidence interval [CI]: 1.02–1.08, P>0.01). The majority of identified TBE cases occurred between April and October, consistent with the seasonality of tick activity. Areas with IR greater than 10 per 100,000 appear to be concentrated in 3 main

foci: 1 in the Autonomous Province of Trento (IR=41.6), 1 in the Belluno Alps in Veneto (IR=35.9), and the third at the extreme northeast section of Friuli-Venezia Giulia (IR=42.6).³ According to this study, the risk of TBE is associated with altitude, with the highest values found for municipalities between 400 and 600 m a.s.l., and the IR falling along with municipality altitude decrease or increase. Of note, the IR for municipalities with a mean altitude >800 m a.s.l. appears to be 5 times higher than for municipalities with a mean altitude <200 m a.s.l.³

A national TBE surveillance system recording neuro-invasive TBEV infections was established since 2017. In 2020, the number of notified cases reached a record, with 55 cases mainly from four northeastern Italian regions and provinces: Trento, Bolzano, Friuli-Venezia Giulia and Veneto (Fig. 3). In addition to these well-known positive areas, another two regions were added although they reported intermittent sporadic cases, namely Emilia Romagna with 2 cases in 2020 and Lazio with 1 case in 2019 (Fig. 3). Average annual incidence per 100.000 inhabitants doubled its value from 0.77 in 2017 to 1.42 in 2020. In particular, the province of Trento showed a sharp increase in the incidence since 2012, despite vaccination efforts. To assess the current risk of infection in the provincial territory, an integrated one-health research approach was applied, combining the analysis of the distribution of human cases, the study of seroprevalence in sentinel hosts (goats) and the direct screening of questing ticks.¹⁶ A total of 1.56% of goats resulted positive for specific antibodies for TBEV. Sampling of ticks was concentrated in areas where TBEV circulation was observed both in seropositive goats or in humans, resulting in a prevalence of 0.17%. In particular these results revealed an increased prevalence of TBEV in ticks and the emergence of new active TBE foci which are located northward and at higher altitude (1.109 m a.s.l.) compared to previous investigations. None of the areas with seropositive goats was confirmed by TBEV detection in ticks and recent human cases, but this aspect needs further confirmation.

The observed increase of TBE cases was associated with the expansion of tick populations resulting from climatic factors, increasing abundance of ungulates, and changes in human behavior and land use, in addition to increased recognition and reporting of TBE cases.²²⁻²³ Although the

distribution of human cases is consistent with that of the competent tick vector, the widely dispersed distribution of ticks in the environment and their very low TBEV prevalence (usually below 1%), make them an unsuitable indicator of TBEV infection risk. For these reasons, entomological studies, even if performed in endemic regions, cannot be translated into a direct human risk, and other factors should be considered in order to address public health efforts toward TBE hazard. For example, since the 1990s, rising cervid population numbers and changes in forest structure in the northeastern regions and provinces of Italy were observed in conjunction with an increase in TBE incidence,²² but this relationship is not always positive and at a threshold density level of ungulates TBEV prevalence decreases.²⁴ Transmission of TBEV from infected nymphs to co-feeding uninfected ticks on rodents is considered the most efficient route for this virus, therefore, studies regarding the ecological and abiotic conditions affecting tick feeding dynamics are important. Recently a long-term longitudinal field study highlighted that the autumnal cooling rate and the presence of roe deer and mice are crucial ecological drivers for co-feeding transmission which in turn reflect in the maintenance of a TBE hotspot.²⁵

Vaccination for TBE is currently recommended in Italy among residents and occupationally exposed groups, in particular in rural endemic areas.¹⁷ In affected regions and provinces, TBE is offered free of charge to risk groups and the resident population since 2013 in Friuli-Venezia Giulia and since 2018 in the Autonomous Provinces of Trento and Bolzano. Affected regions and provinces have also made information on TBE vaccination available on websites.¹⁸⁻²¹

In conclusion, the incidence of TBE in Italy is relatively low and the risk appears to be geographically restricted to the pre-alpine and alpine regions of the country. More studies are necessary to disentangle the complex factors that are involved in the circulation and maintenance of TBEV in an endemic focus and early-warning predictors should be better assessed. Human cases are currently reported from northeastern regions (Friuli-Venezia Giulia, Veneto and in the Provinces of Trento and Bolzano), with the highest incidence rates being reported in areas between 400 and 600 m a.s.l. TBE vaccine is offered to residents living in high-risk areas, but its impact on disease occurrence in the affected communities is not yet evaluated.

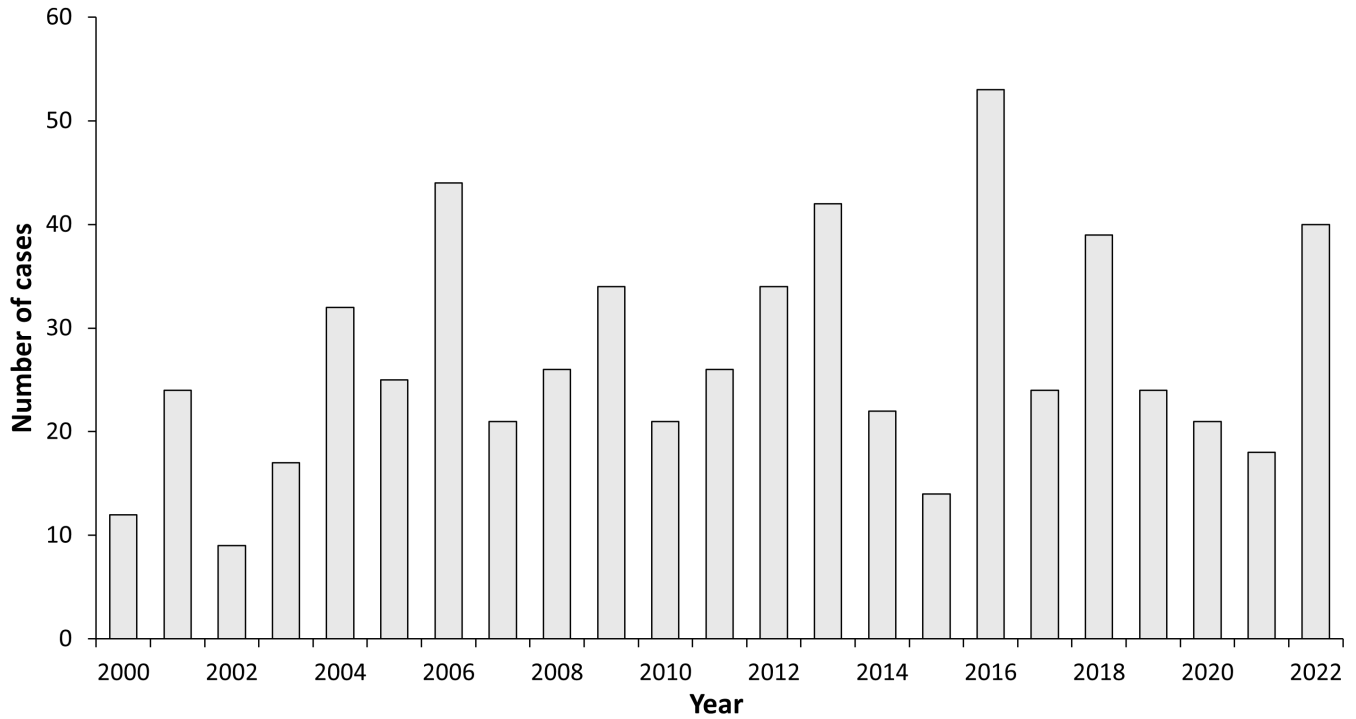
Overview of TBE in Italy

Table 1: Virus, vector, transmission of TBE in Italy (northeastern)

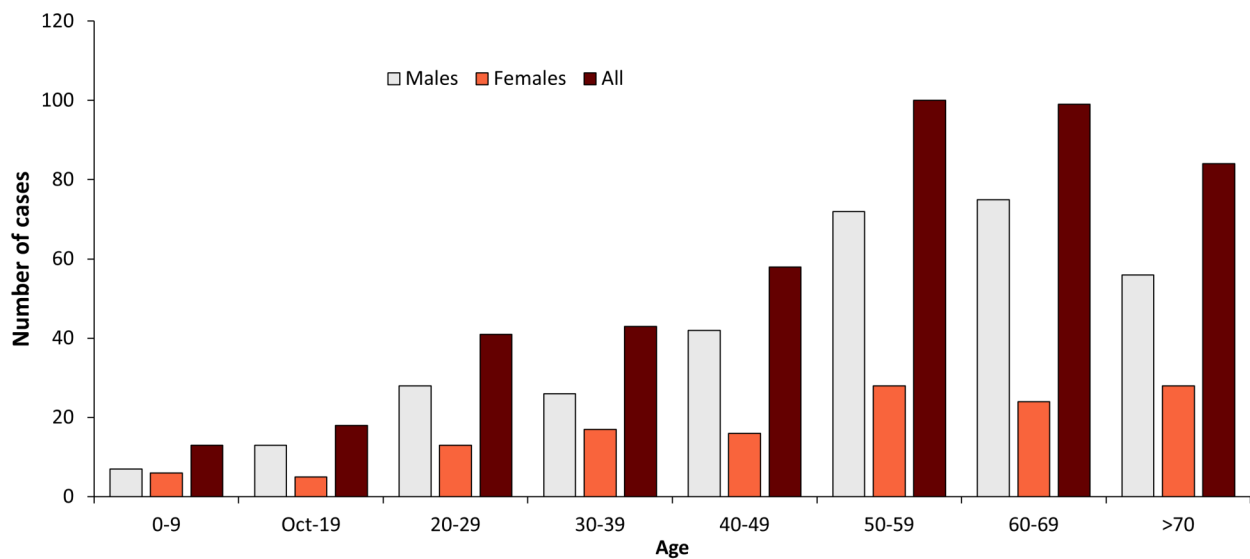
Viral subtypes, distribution	European TBEV subtype; northeast regions: Friuli-Venezia Giulia, Veneto, Trentino-Alto Adige (Fig. 3)
Reservoir animals	Ticks and small rodents. Consumption of milk and milk products from infected goats, sheep, or cows
Infected tick species (%)	<i>I. ricinus</i>
Dairy product transmission	Not documented

Table 2: TBE-reporting and vaccine prevention in Italy (northeastern)

<p>Mandatory TBE reporting^{16,6}</p>	<p>Reported by Department of Infectious Diseases, National Institute of Health, Italy in collaboration with all the Infectious Diseases Units and Public Health Districts.</p> <p>Case definition: clinical criteria are any symptoms of inflammation of the CNS (for example, meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis). A TBE case is confirmed by at least one of the following five laboratory criteria: TBE specific IgM AND IgG antibodies in blood; TBE specific IgM antibodies in CSF; seroconversion or four-fold increase of TBE-specific antibodies in paired serum samples; detection of TBE viral nucleic acid in a clinical specimen; isolation of TBE virus from clinical specimen.</p> <p>Surveillance has been enhanced at the national level since 2017.</p>
<p>Special clinical features¹³⁻¹⁵</p>	<p>Biphasic disease is not reported.</p> <p>At-risk groups are defined by occupational risk (i.e. agricultural workers and forest or lumber workers) or risk hobbies (i.e. hiking/trekking, mushroom foraging).</p> <p>Presumed place of exposure and date of tick bite are recorded.</p> <p>Sequelae (information available on 193 cases): 18.1% with permanent sequelae, and 28.5% with temporary sequelae.</p> <p>Case-fatality rate: 0.7%</p>
<p>Available vaccines</p>	<p>TICOVAC 0.5 mL (Pfizer Srl)</p>
<p>Vaccine recommendations and reimbursement, and uptake by age group/risk group/ general population</p>	<p>Friuli-Venezia Giulia: vaccination is free of charge for residents.</p> <p>Veneto: vaccination is not free of charge; recommended for those who live in the woods or in rural areas at risk for TBE.</p> <p>Trentino-Alto Adige: vaccination is free of charge for residents.</p>
<p>Name, address/website of TBE National Reference Center</p>	<p>Prof. Giovanni Rezza Dipartimento Malattie Infettive Istituto Superiore di Sanità Viale Regina Elena, 299 00161 Roma, Italia</p> <p>Website: https://www.iss.it/?p=27</p>

Figure 1: Reported human cases of TBE, Italy, 2000–2022²⁶⁻²⁸

**Data on vaccination rate : Appendix—Figure 1*

Figure 2: Age and gender distribution of reported human cases of TBE, Italy, 2000–2016

Source Data: Appendix—Figure 2

Figure 3: Regions in northeastern Italy reporting TBE cases
(BZ=Autonomous Province of Bolzano; TN=Autonomous Province of Trento;
[BZ+TN=Trentino-Alto Adige] VEN= Veneto; FVG= Friuli-Venezia Giulia
ER=Emilia Romagna; L=Lazio)



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Appendix

Source data: Figure 1

Year	Number of cases	Incidence/10 ⁵	Vaccination rate (%)
2000	12	0.021	
2001	24	0.042	
2002	9	0.016	
2003	17	0.029	
2004	32	0.055	
2005	25	0.043	
2006	44	0.074	0.11
2007	21	0.035	0.11
2008	26	0.043	0.11
2009	34	0.056	0.14
2010	21	0.035	0.13
2011	26	0.044	0.16
2012	34	0.057	0.10
2013	42	0.069	0.18
2014	22	0.036	0.15
2015	14	0.023	
2016	53	0.087	
2017*	24	0.04	
2018*	39	0.065	
2019*	24	0.04	
2020*	21	0.035	
2021**	18	0.03	
2022***	40	0.068	

* Neuroinvasive laboratory confirmed TBEV infections

** 18 total with 4 imported cases

*** Total cases from January 1, 2022 to October 31, 2022

Note: Data on vaccine coverage are not available for 2015–2022

Source data: Figure 2

Age group (years)	Males	Females	All
0-9	7	6	13
10-19	13	5	18
20-29	28	13	41
30-39	26	17	43
40-49	42	16	58
50-59	72	28	100
60-69	75	24	99
>70	56	28	84

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