

TBE in Italy

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History and Current Situation

Italy is considered a low incidence country for tick-borne encephalitis (TBE) in Europe¹. Areas at higher risk for TBE in Italy are geographically clustered in the forested and mountainous regions and provinces in the north east part of the country, as suggested by TBE case series published over the last decade²⁻⁵. A national enhanced surveillance system for TBE has been established since 2017⁶. Before this, information on the occurrence of TBE cases at 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 literature¹.

TBE has been recorded in Italy since 1967, with foci of infection in north east (Trento, Belluno and Gorizia) and central Italy (Florence and Latina) provinces⁷⁻¹⁰. TBE presence in central Italy has not been confirmed by further studies on ticks and serosurveys conducted afterwards¹¹⁻¹², suggesting the extinction 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 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 Giulia¹³, Trento province¹⁴ and Turin province¹⁵, respectively. Interestingly, Turin province has never reported human cases of TBEV infection, so far.

A retrospective study conducted in 2015 in the north east regions, allowed the identification of 367 cases (0.38 per 100,000 inhabitants) during the period from 2000 to 2013³. 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 north east 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.

In 2018, the recently established national TBE surveillance system recorded a total of 40 confirmed cases of neuro-invasive TBEv infection in four north eastern Italian regions and provinces: Trento, Bolzano, Friuli-Venezia Giulia and Veneto. Incidence ranged from 0.16 per 100,000 in Friuli-Venezia Giulia to 1.48 in the Trento province where, regional surveillance has detected increases in the annual number of TBE cases, with transmission spreading outside the historically recognised foci^{5,16}.

Vaccination for TBE is currently recommended in Italy among residents and professionally exposed groups, in particular in rural endemic areas¹⁷. 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 websites¹⁸⁻²¹.

TBE increase has been shown to be associated with the expansion of tick populations resulting from climatic factors, increasing abundance of ungulates, and changes in human behaviour and land use, in addition to increased recognition and reporting of TBE cases²²⁻²³. Although the distribution of human cases is consistent with that of the competent tick vector, the overdispersed 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 '90s, rising cervid population numbers and changes in forest structure in the north-eastern regions and provinces of Italy were observed in conjunction with an increase in TBE incidence²², but this relationship is not always positive and at a threshold density level of ungulates TBEV prevalence decreases²⁴. Also seroprevalence in domestic animals, showed a good spatial correlation with TBE incidence in humans and might also uncover presently unknown TBEV foci distribution²⁵.

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 (TICOVAC) is offered to resident people living in high-risk areas, but its impact on disease occurrence in the affected communities is not yet evaluated.

Overview of TBE in Italy

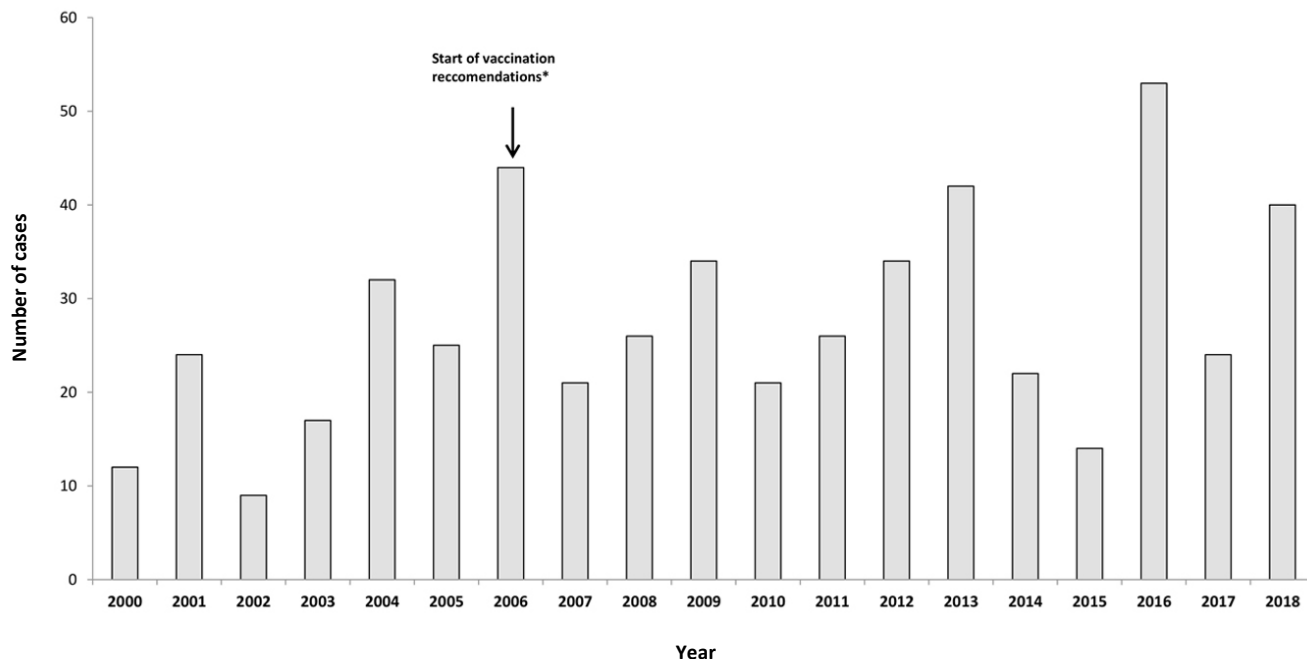
Table 1: Virus, vector, transmission of TBE in Italy (northeastern)

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

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

Mandatory TBE reporting ^{16,6}	Reported by Department of Infectious Diseases, National Institute of Health, Italy in collaboration with all the Infectious Diseases Units and Public Health Districts. Case definition: Clinical criteria are any symptoms of inflammation of the CNS (for example, meningitis, meningo-encephalitis, 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. Surveillance has been enhanced at national level since 2017.
Special clinical features ¹³⁻¹⁵	Bi-phasic disease is not reported 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) Presumed place of exposure and date of tick bite are recorded
	Sequelae (information available on 193 cases): 18.1% with permanent sequelae, and 28.5% with temporary sequelae Case-fatality rate: 0.7%
Available vaccines	TICOVAC 0.5 mL (Pfizer Srl)
Vaccine recommendations and reimbursement, and uptake by age group/risk group/ general population	Friuli-Venezia Giulia: Vaccination is free of charge for residents. Veneto: Vaccination is not free of charge. Recommended for those who live in the woods or in rural areas at risk for TBE. Trentino-Alto Adige: Vaccination is free of charge for residents.
Name, address/website of TBE National Reference Center	Prof. Giovanni Rezza Dipartimento Malattie Infettive Istituto Superiore di Sanità Viale Regina Elena, 299 00161 Roma, Italia Website: https://www.iss.it/?p=27

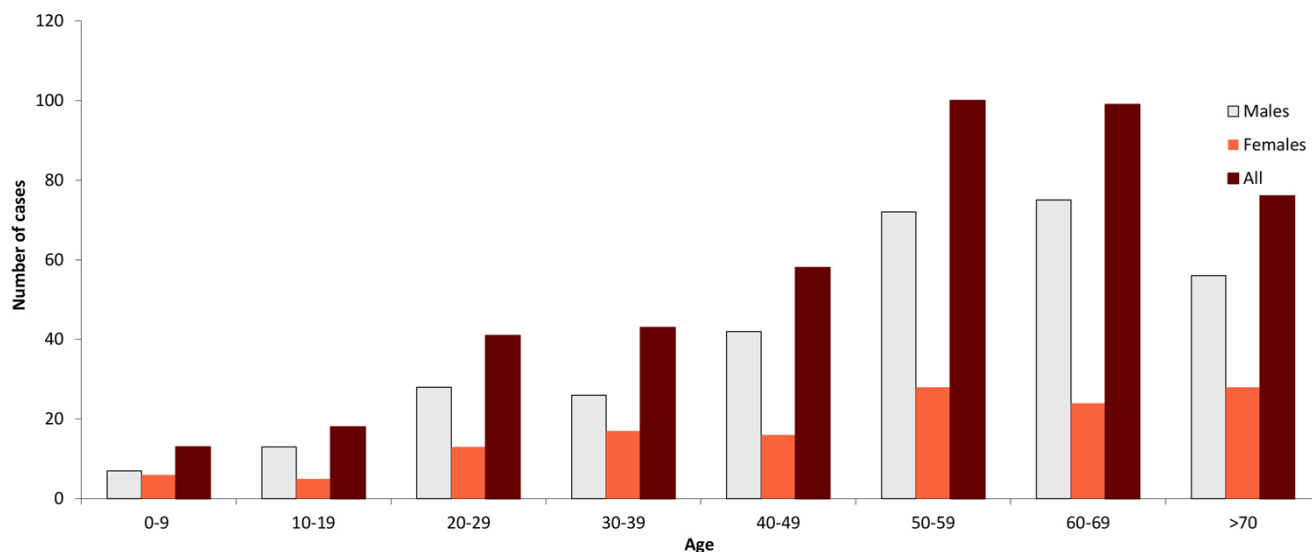
Figure 1: Reported human cases of TBE, Italy, 2000-2018.



Source: <http://demo.istat.it/>

*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).



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Appendix

Source data: Figure 1

Year	Number of cases	Incidence/ 10 ⁵	Vaccination rate (%)
2000	12	0.20	
2001	24	0.41	
2002	9	0.15	
2003	17	0.29	
2004	32	0.53	
2005	25	0.41	
2006	44	0.72	0.11
2007	21	0.34	0.11
2008	26	0.42	0.11
2009	34	0.55	0.14
2010	21	0.34	0.13
2011	26	0.42	0.16
2012	34	0.54	0.10
2013	42	0.67	0.18
2014	22	0.35	0.15
2015	14	0.22	
2016	53	0.84	
2017*	24	0.38	
2018*	40	0.63	

*Neuro-invasive laboratory confirmed TBEV infections

Note: Data on vaccine coverage are not available for 2015-2018

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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