

Epidemiology of Tick-borne encephalitis in North-Eastern Italy (2017-2020): international insights from national notification reports

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To the Editor,

Italy is usually considered as a low-risk country for Tick Borne Encephalitis (TBE), a potentially severe disorder caused by the flavivirus TBE virus (TBEV) (1,2). Endemicity for TBEV is historically restricted to the North-Eastern Regions of “Triveneto” (i.e. autonomous provinces of Trento [APT] and Bolzano [APB], and the regions of Veneto, and Friuli-Venezia-Giulia; total area 39,875.87 km²; total population 7,163,418 inhabitants according to 2020 census), with a notification rate estimated in 0.38 cases per 100,000 during the time period 2000-2013 (1,3).

Even though national estimates are substantially below the cut-off value of 5 cases per 100,000 that recommend active vaccination policies for the general population (1,2,4), overall incidence is on the rise, mirroring the pan-European trend (5,6). The causes reasonably include a mixture of environmental (e.g. climate changes) and behavioral factors that eventually increase the likelihood of human interactions with a competent vector (i.e. *Ixodes spp*) from areas where the pathogen highly circulating in appropriate hosts (i.e. rodents and ungulates) (3,4).

In this regard, we think that a retrospective analysis of annual reports from Italian National Health Institute (Istituto Superiore di Sanità, or ISS; <https://www.epicentro.iss.it/arbovirosi/bollettini>) (7) may shed some insights on the ongoing epidemiology of TBEV in Italy.

According to official figures, a total of 103 Italian cases occurred between 2017 and 2020, 100 of them

in the Triveneto, with a pooled incidence rate (IR) of 0.35 per 100,000 [95%CI 0.28-0.42] (**Figure 1**). Annual estimates peaked in 2018 (0.54 per 100,000 [95%CI 0.39-0.74]), but overall figures remain quite low, in particular when compared to nearby countries likewise Austria (399 cases, mean IR 1.51 per 100,000) or Slovenia (366 cases, mean IR 4.61 per 100,000), and Switzerland (377 cases reported in 2018 alone; crude IR 4.41 per 100,000) (8). However, such figures require some comments.

Firstly, ISS bulletins report only on TBE cases characterized by meningitis and/or encephalitis, similarly to the figures reported by Austria and Slovenia, while Switzerland authorities usually report on all newly diagnosed infections, irrespective of complained symptoms (7,8). In facts, only 20% to 30% of all TBEV infections usually evolve in CNS involvement (1,2).

Second, the mandatory reporting systems reportedly failed to recall a large share of patients (up to 45%) if hospital discharge data were not appropriately integrated (2). In other words, it is reasonable that Italian figures may largely underestimate actual epidemiology of TBEV, particularly for the endemic areas of Triveneto (1,2). Supposing a dropout rate of 45%, and assuming that TBE cases with CNS impairment would represent no more than 30% of actual TBEV infections, actual Italian burden between 2017 and 2020 may be estimated to 152 cases/year (95%CI 59.7-243.3) for Triveneto alone, with an IR equals to 2.8 per 100,000, i.e. an estimate approximating aforementioned figures for Switzerland in 2018.

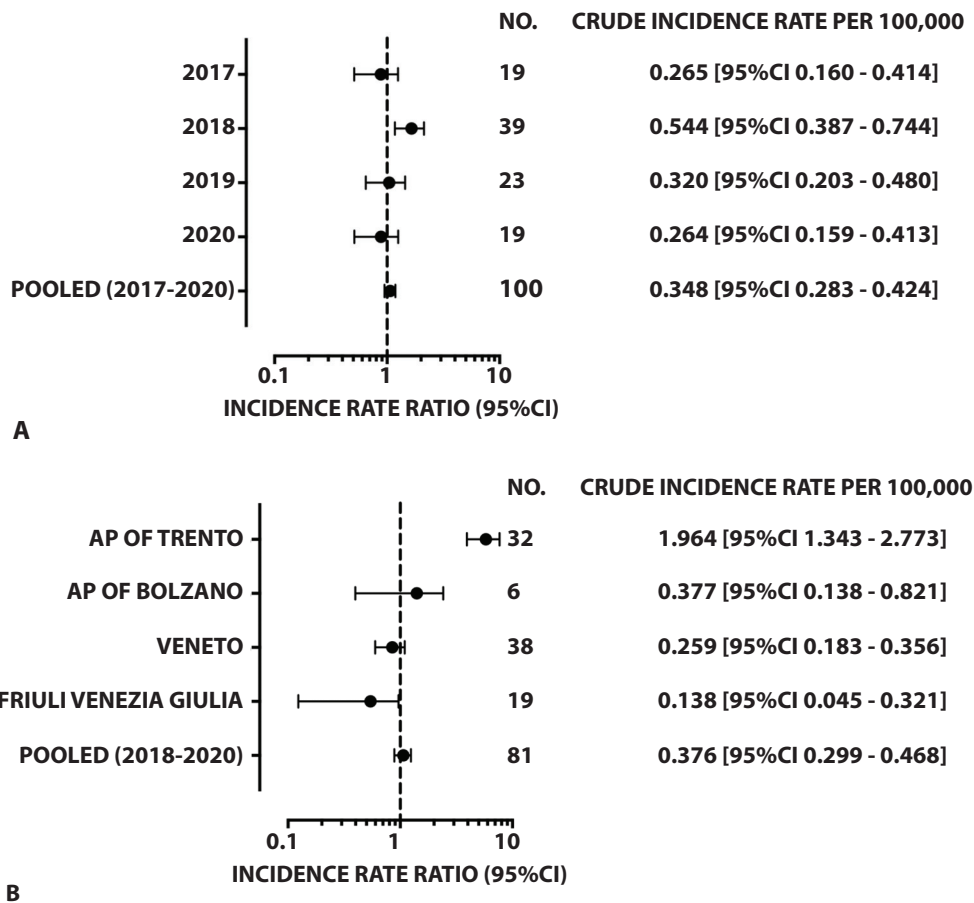


Figure 1. Incidence Rate and Incidence Rate Ratio for TBE cases characterized by central nervous system involvement in the Triveneto (i.e. Autonomous Provinces of Trento and Bolzano; regions of Veneto and Friuli-Venezia-Giulia; total area of 39,875.87 km²; total population 7,163,418 inhabitants according to 2020 census) between 2017 and 2020, by year (a) and area (b) of notification. Data were retrieved from official bulletins of the Italian National Health Institute (ISS), and are available from <http://www.epicentro.iss.it/arbovirosi/bollettini>. Crude incidence Rates and Incidence Rate Ratio were calculated assuming the estimate of 0.38/100,000 inhabitants (1), by means of R version 4.0.3 (R Core Team, 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.Rproject.org/>), and RStudio (version 1.2.5019) software, package epiR.

Third, pooled Italian figures mask something alike “a tale of two stories”. On the one hand, during the time period 2018 – 2020, Veneto, Friuli-Venezia-Giulia, and APB, exhibited incidence rates were alike the overall estimates for 2000 – 2013 (Figure 1). For example, IR for Friuli-Venezia-Giulia was 0.14 per 100,000 [95%CI 0.04-0.32], with a corresponding incidence rate ratio (IRR) of 0.44 [95%CI 0.19-1.01] compared to overall figures for 2000-2013. On the other hand, despite the active vaccination campaigns put in place by the local Authorities (4), estimates for the APT

peaked to 1.96 cases per 100,000 [95%CI 1.34-2.77], with an IRR equals to 5.63 [95% 4.02-7.76].

As available evidence suggests that the majority of APT cases are clustered in some foci of hyperendemicity for TBEV-infected ticks (1,9), a possible explanation for these results may be found through the “one health approach”, i.e. by summarizing environmental data with evidence from human and veterinary medicine. In facts, the mountainous territories of the APT, have become a popular holiday destination for Italian and foreigner tourists (4), but mostly represent

appropriate habitats for both tick vectors and usual hosts for TBEV, and particularly ungulates (9). Interestingly, their number remained substantially stable in the APT until the 2005, roughly doubling in the following decade (10). That leads to increasingly interactions between humans and wild animals, and such a trend was somewhat mirrored by the increasing occurrence of TBEV infections (1,3,4,9).

Finally, the TBEV strain isolated in APT is only distantly related to the those from other areas of Triveneto, rather belonging to the TBEV-Eu subtype that is highly circulating in Central Europe since 2012 (9). TBEV-Eu has been identified in migratory birds, including those hosted on their route by the forests of APT. If the migratory birds are the key player in the spreading of TBEV-Eu across Europe, their migration could in turn explain the heterogeneity of APT compared not only to bordering countries of Austria and Slovenia, but also to the nearby APB. In turn, such features suggest that TBEV-Eu could rapidly spread even in areas not usually associated with TBEV endemicity, not only in Italy but also in Southern Europe.

Therefore, Italian data stress the potentially extensive underestimation for TBEV infections, at least in North-Eastern region, and the significance of TBEV-Eu strain in the epidemiology of TBE emphasizes the importance for appropriate surveillance of TBE cases, also in terms of genetic analysis.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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