High habitat richness reduces the risk of tick-borne encephalitis in Europe: A multi-scale study

1 ***Title:*** **High habitat richness reduces the risk of tick-borne encephalitis in Europe: a**

2 **multi-scale study.**

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[1] HRI: Habitat Richness Index

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22 ***Abstract***

23 *Background:* The natural transmission cycle of tick-borne encephalitis (TBE) virus is

24 enhanced by complex interactions between ticks and key hosts strongly connected to

25 habitat characteristics. The diversity of wildlife host species and their relative abundance is

26 known to affect transmission of tick-borne diseases. Therefore, in the current context of

27 global biodiversity loss, we explored the relationship between habitat richness and the

28 pattern of human TBE cases in Europe to assess biodiversity's role in disease risk

29 mitigation.

30 *Methods:* We assessed human TBE case distribution across 879 European regions using

31 official epidemiological data reported to The European Surveillance System (TESSy)

32 between 2017 and 2021 from 15 countries. We explored the relationship between TBE

33 presence and the habitat richness index (HRI[1]) by means of binomial regression. We

34 validated our findings at local scale using data collected between 2017 and 2021 in 227

35 municipalities located in Trento and Belluno provinces, two known TBE foci in northern

36 Italy.

37 *Findings:* Our results showed a significant parabolic effect of HRI on the probability of

38 presence of human TBE cases in the European regions included in our dataset, and a

39 significant, negative effect of HRI on the local presence of TBE in northern Italy. At both

40 spatial scales, TBE risk decreases in areas with higher values of HRI.

41 *Interpretation:* To our knowledge, no efforts have yet been made to explore the

42 relationship between biodiversity and TBE risk, probably due to the scarcity of high-

43 resolution, large-scale data about the abundance or density of critical host species. Hence,

44 in this study we considered habitat richness as proxy for vertebrate host diversity. The

45 results suggest that in highly diverse habitats TBE risk decreases. Hence, biodiversity loss

46 could enhance TBE risk for both humans and wildlife. This association is relevant to

47 support the hypothesis that the maintenance of highly diverse ecosystems mitigates

48 disease risk.

49 **Keywords:** Biodiversity, Europe, Habitat Richness, One Health, Vector-borne disease,

50 Tick-borne encephalitis

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Introduction

Tick-borne encephalitis (TBE) is one of the most severe tick-transmitted diseases in Eurasia, with more than 3000 confirmed cases reported annually in Europe [1]. During the last decade, European incidence of TBE human cases increased significantly from 2412 confirmed cases in 2012 to 3604 confirmed cases in 2020, concomitantly with a north-westerly spread [2] and the appearance of new foci of infection in previously non-endemic countries [3], making TBE a growing Public Health challenge in Europe.

TBE virus (TBEV) is a flavivirus that affects the central nervous system. It is transmitted mainly through the bite of ticks belonging to the *Ixodes ricinus* complex, such as *I, ricinus* and *I. persulcatus* [4], but can also be acquired through consumption of infected unpasteurized milk and dairy products [5].

The active circulation of TBEV among vectors and reservoir hosts occurs in specific hotspots and strongly depends on the co-occurrence of multiple ecological factors, such as abiotic conditions - which, in turn, determine vectors' activity and habitat suitability [6,7] - along with a subset of key vertebrate host species [8–10]. Tick larvae mainly feed on small mammals, nymphs feed on small- and medium-sized mammals, birds, and reptiles, and adults feed on large animals such as ungulates [11]. Ticks are both vectors and main viral reservoirs, remaining infected throughout their life cycle due to transstadial and transovarial transmission. Uninfected ticks can also acquire the infection via systemic transmission, while feeding on a viremic competent host, or via non-systemic transmission, while co-feeding with infected ticks [12,13].

Various animal species can act as dead-end hosts or maintain and amplify the virus (reservoir hosts), with or without evident symptoms of the disease. Rodents and

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93 insectivores are considered the main reservoir hosts for TBEV maintenance and

94 circulation. Once infected with TBEV, they may develop a chronic infection, although the

95 duration of viraemia, and thus their infectivity to ticks, is commonly considered short (two

96 to nine days) [14]. Symptoms and viremia have been rarely detected in wild ungulates [15],

97 which are not competent for viral transmission, although they are important hosts for the

98 amplification of tick populations [16,17].

99 The diversity of wildlife host species and their relative abundance is known to affect

100 transmission of tick-borne diseases such as Lyme disease [18–20]. This relationship,

101 denoted as *diversity-disease relationship*, might also apply to the TBEV transmission

102 system, as the main TBEV vector, *I. ricinus,* parasitizes several different host species [21]

103 and its infection prevalence is likely to be affected by host diversity and competence

104 among hosts. Rodent species such as *Apodemus flavicollis* and *Clethrionomys glareolus*

105 are considered the main reservoir hosts for TBEV circulation [22,23] as they

106 simultaneously harbour multiple developmental stages of ticks [9,12]. Nonetheless,

107 Apodemus spp. support higher tick burdens (Kiffner et al. 2011), higher tick- feeding

108 success, and a more efficient TBEV transmission via co-feeding compared to C. glareolus

109 [12].

110 Little is known about the effects of habitat and vertebrate host diversity on the emergence

111 of tick-borne diseases in Europe, given the complexity of their transmission dynamics.

112 Moreover, the lack of high-resolution, large-scale data on the abundance or density of key

113 vertebrate host species, such as rodents and ungulates, is one of the main reasons why

114 no attempt has been made to investigate the relationship between biodiversity and TBE

115 risk in both local and large-scale geographical contexts. So far, few studies explored the

116 interactions between ticks, vertebrate hosts, habitat and tick-borne pathogens in Europe

117 [24–26]. To our knowledge, no studies have investigated the relationship between TBE

118 and biodiversity in Europe.

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119 In this study we relied on the habitat richness index (HRI), a novel indicator that accounts

120 for the diversity of European ecosystem types (sensu "Habitat Directive" - Council

121 Directive 92/43/EEC). Habitat diversity, measured as the number of different habitats in a

122 given area, has proven to be a prominent driver for species diversity of a variety of taxa at

123 the landscape scale [27]. Indeed, the use of habitat amount in an equal-sized sample sites

124 as biodiversity proxy is contextualized by the habitat amount hypothesis [28] and habitat

125 richness or heterogeneity can be used as an explanatory variable for biodiversity modeling

126 [29–31]. Furthermore, Habitat Directive types monitoring is the standardized and legally

127 established tool for monitoring ecosystems in Europe (Council Directive 92/43/EEC).

128 Considering the need for a broad and scale-dependent understanding of the diversity-

129 disease relationship [32] we applied HRI for the first time to evaluate its relationship with

130 the occurrence of human TBE cases in Europe and in a local setting located in the

131 northern-Italian provinces of Trento and Belluno, which are well known endemic areas for

132 TBE [33].

133 **Methods**

134 **Study areas**

135 We carried out the statistical analysis at two different spatial scales, using regional-level

136 data about TBE distribution and HRI across 15 European countries, i.e., "analysis at

137 European scale", and municipal-level TBE and HRI data in two northern Italian provinces,

138 Trento and Belluno, i.e., "analysis at local scale".

139 **Epidemiological data**

140 For the analysis at European scale, data for laboratory-confirmed human TBE cases were

141 provided by the European Surveillance System (TESSy) and released by ECDC. They

142 included, when available, the probable place of infection at NUTS-3 (Nomenclature of

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143 territorial units for statistics, small regions for specific diagnosis) or NUTS-2 level

144 (Nomenclature of territorial units for statistics, basic regions for the application of regional

145 policies). In our study, we used cases reported to TESSy between 2017 and 2021, since

146 the place of infection was unknown or not recorded in most countries prior to 2017.

147 Patients infected abroad or whose location of exposure was unknown or not provided at

148 high spatial resolution, were excluded. Only countries that reported the place of infection at

149 the NUTS-3 or NUTS-2 level for at least 75% of the cases notified over the selected period

150 were included. The 13 countries selected according to these criteria were: Austria, Czech

151 Republic, Denmark, Germany, Finland, France, Hungary, Italy, Lithuania, Poland,

152 Romania, Slovakia, and Sweden. To take into consideration areas with no recorded TBE

153 presence, we included two countries with no autochthonous cases reported during the

154 study period, namely Spain and Ireland.

155 Additionally, to perform the analysis at local scale, we used municipal-level human TBE

156 cases recorded in the Trento and Belluno Provinces (Italy) from 2017 to 2021. These data

157 were provided by local Public Health Agencies, Azienda Provinciale per i Servizi Sanitari

158 Provincia Autonoma di Trento (APSS) and Unità Locale Socio Sanitaria Dolomiti (ULSS1).

159 Based on these data sources, we compiled two different dichotomous datasets ,depicting

160 the presence and absence of human TBE cases, at European (Figure 1a) and at local

161 scale (Figure 3a).

162 **Ecological variables**

163 The habitat richness index (HRI) was derived from the habitat distribution maps of 222

164 terrestrial habitats of community interest, obtained from the European Environment

165 Agency [34] and based on the standard grid provided by EEA for habitat monitoring with a

166 spatial resolution of 10 km (for more details on the computation of this index see [27]). HRI

167 can be considered a proxy for biodiversity, as it is positively correlated with the richness of

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168   the species listed in the Annex species of the Birds and Habitats Directives [27]. For our

169   analysis, we used the normalized index (*i.e.*, habitat richness corrected for actual cell

170   area), which values ranged from 0 to 1·5. To exclude potential extreme values, we

171   computed the 95-th percentile value of HRI as a measure of the levels of biodiversity that

172   characterize each spatial unit, in accordance with the spatial resolution of the available

173   official epidemiological data provided by ECDC and local Public Health Agencies.

174   To assess the distribution of key vertebrate species across the European NUTS-2 and

175   NUTS-3 regions included in our study, we used 1-km data about the probability of

176   presence of critical TBEV reservoir and tick-amplification hosts (*i.e.,* rodents, *Apodemus*

177   *flavicollis* and *Clethrionomys glareolus,* and cervids, *Dama dama*, *Capreolus capreolus*

178   and *Cervus elaphus*) that were previously derived using long established ensembled

179   Random Forest and Boosted Regression Trees based spatial modeling techniques, as

180   described in [35].

181   **Statistical analysis**

182   We used binomial regression to describe the association between the occurrence of

183   human TBE cases and HRI, at the two different spatial scales. For each epidemiological

184   dataset, we considered models with both linear and quadratic covariate of the form:

185   $\log(p/(1\text{-}p)) = a_0 + a_1 HRI + a_2 HRI^2 + \varepsilon$

186   where *p* represents the probability of presence of at least one human TBE case, a_0, a_1 and

187   a_2 are the model coefficients, ε is the random error component, and *HRI* indicates the 95-

188   th percentile value of habitat richness (Table 1).

189   We tested both linear and quadratic models and ranked their performances based on the

190   Akaike's Information Criterion (AIC) score [36]. Spatial autocorrelation was detected

191   through Moran's I statistic and visual inspection of Moran's scatterplot [37] and was filtered

192   out by including an autocovariate term that represents spatial dependence in the model

193   residuals [38]. In residuals autocovariate (RAC) models, spatial autocorrelation is

194   accounted for by estimating the strength of the relationship between the model residuals

195   and the values of those residuals at neighboring locations. This procedure leads to an

196   autocovariate that captures only the variance unexplained by explanatory variables and

197   therefore the RAC model better captures the true influence of these covariates, resulting in

198   strong inferential performance [38]. Moreover, models with autocovariates typically provide

199   unbiased estimates of fixed effects [39].

200   The strength of the correlation between HRI and the probability of presence of rodents and

201   cervids across Europe was assessed using Pearson's correlation coefficient.

202   All analyses were performed using the statistical software R ver. 4.1.2 [40] and packages

203   spdep [41], raster [42], and sf [43].

204   **Results**

205   **Analysis at European scale**

206   Based on the data released by ECDC, the current geographical distribution of human TBE

207   cases in Europe extends to the west as far as the French region of Alsace, to the south as

208   far as northern Italy and to the east as far as the Balkan countries and northward to

209   Norway and Finland. During the period 2017-2021, 13 European countries (Austria, Czech

210   Republic, Denmark, Germany, Finland, France, Hungary, Italy, Lithuania, Poland,

211   Romania, Slovakia, and Sweden) reported at least one locally acquired human TBE case

212   with known place of infection at NUTS-3 or NUTS-2 level, for a total of 381 different

213   regions and 12,296 cases. The same countries reported no TBE cases from the remaining

214   442 regions, to which we added 56 regions from Ireland and Spain, for a total of 498

215   regions with no autochthonous cases reported (Figure 1a). The corresponding 95-th

216   percentile values of HRI showed large variations across the continent (Figure 1b). Lower

217   values were found in the agricultural plains of western France, and in the lowland plains of

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218 Poland and Romania. Conversely, high levels of habitat richness were found in the major

219 European mountain ranges, such as the Alps, the Pyrenees, the Scandinavian mountains,

220 the Apennines, the Central Massif in south-eastern France and the Bohemian Forest

221 highlands along the German-Czech-Austrian border, together with regions located along

222 the coastlines of countries facing the Baltic Sea, featured high levels of habitat richness.
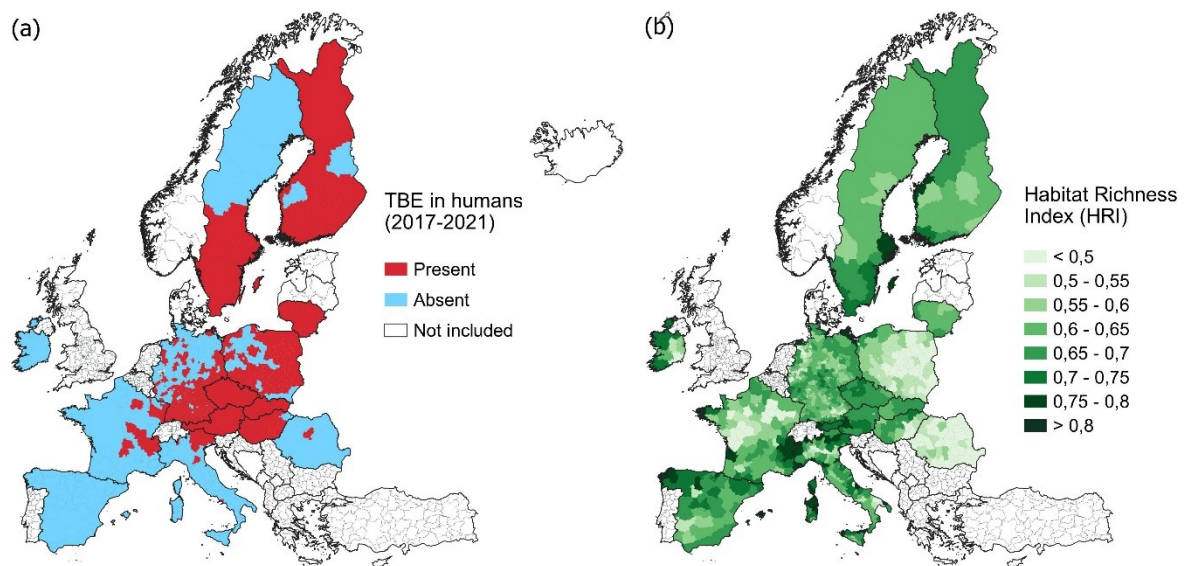
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224 *Figure 1 - Presence of human TBE cases and values of habitat richness index (HRI) in*

225 *Europe. Panel (a): presence in red (n=381) and absence in light blue (n=498) of human*

226 *TBE cases (2017-2021). Panel (b): 95-th percentile value of HRI at regional level.*

227 Our analysis evidenced a significant, parabolic effect of HRI on the presence of human

228 TBE cases in the European regions included in our dataset, as the binomial model with

229 quadratic covariate (AIC = 1010·96) (Table 1) outperformed the linear one (AIC = 1026·3)

230 (Supplementary Table S1).

231 *Table 1 - Results of quadratic binomial regression. The habitat richness index (HRI) and*

232 *autocovariate (ac) were used as predictors, for which the estimated regression*

Predictor	Coefficient	SE	z-value	p-value
Intercept	-8·14	2·22	-3·66	<0·001
HRI	25·06	7·28	3·44	<0·001
HRI^2	-19·69	5·93	-3·32	<0·001
ac	6·22	0·63	9·84	<0·001

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236   Hence, the estimated probability of presence of human TBE cases in Europe showed a

237   humped-shape curve, peaking in regions with intermediate values and then rapidly

238   decreasing and zeroing at lower and higher values of HRI (Figure 2).

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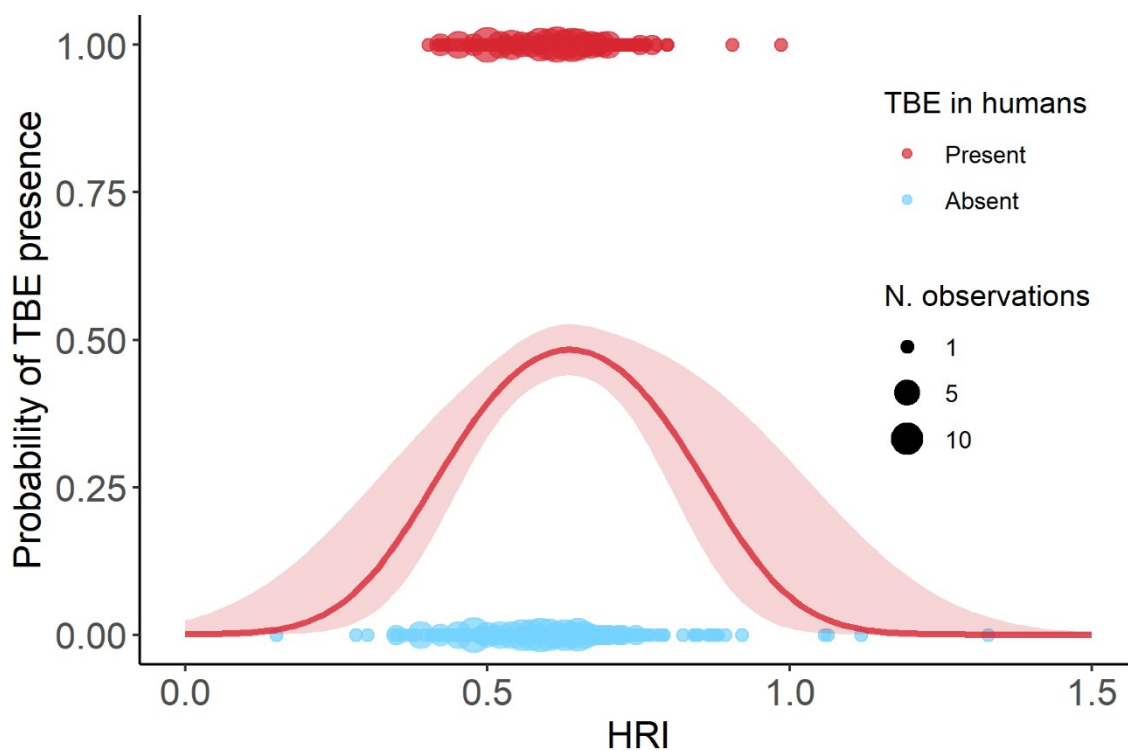
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Figure 2) Estimated probability of TBE presence in Europe based on habitat richness index (HRI). Dots: Observed TBE presence (red) and absence (blue). Line: model prediction. Shaded bands: 95% confidence intervals.

In an analysis of the association between HRI and the probability of presence of key vertebrate hosts, we found a significant negative correlation with the presence of yellow-necked mouse, *A. flavicollis* (r = -0·16, p = 0·006), and a negative, although not significant, correlation with the presence of bank vole, *C. glareolus* (r = -0·06, p = 0·09), roe deer, *C. capreolus* (r = -0·04, p = 0·20) red deer, *C. elaphus* (r = -0·04, p = 0·43), and fallow deer, *D. dama* (r = -0·03, p = 0·44).

Analysis at local scale (Italy)

During the period 2017-2021, 104 and 56 human TBE cases were reported in the Trento and Belluno provinces, respectively. Overall, 73 different municipalities were indicated by patients as the place where they likely acquired the infection during this period (Figure 3a). The entire area is characterized by medium to high values of habitat richness, which peaks in correspondence of natural parks and reserves (Figure 3b).

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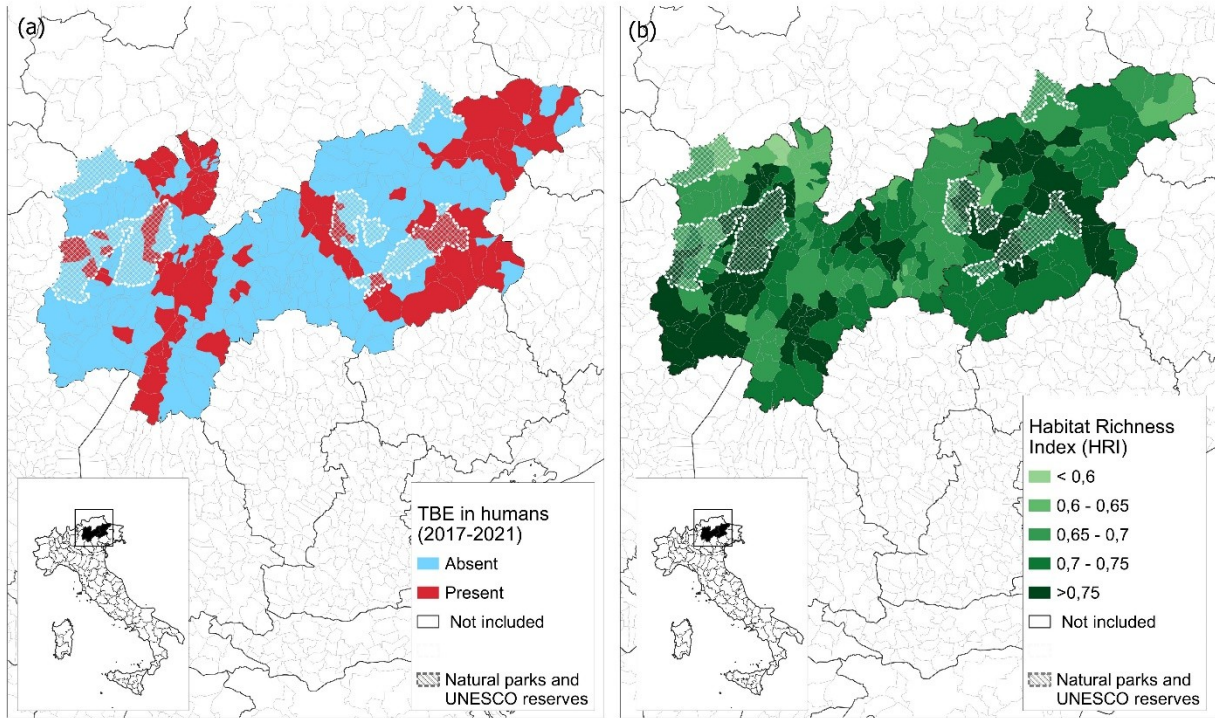
Figure 3 - Presence of human TBE cases and values of habitat richness index (HRI) in

Trento and Belluno provinces (Italy). Panel (a): presence in red (n=73) and absence in

light blue (n=164) of human TBE (2017-2021). Panel (b): 95-th percentile value of HRI at

municipal level.

We found a significant negative association between the levels of HRI in each municipality,

and the corresponding presence of human TBE cases (Table 3).

Table 3 – Results of linear binomial regression. The habitat richness index (HRI) and

autocovariate (ac) were used as predictors, for which the estimated regression

coefficients, standard errors SE, z-values, and p-values are given. Observations =237.

AIC =270·7.

Predictor	Coefficient	SE	z-value	p-value
Intercept	6·34	2·03	3·13	<0·001
HRI	-9·93	2·84	-3·49	<0·001
ac	0·88	0·24	3·68	<0·001

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269 In this case, the probability of presence of human TBE cases is higher in those regions

270 with low to medium values of HRI, and then dramatically decreases as HRI becomes

271 higher (Figure 4).
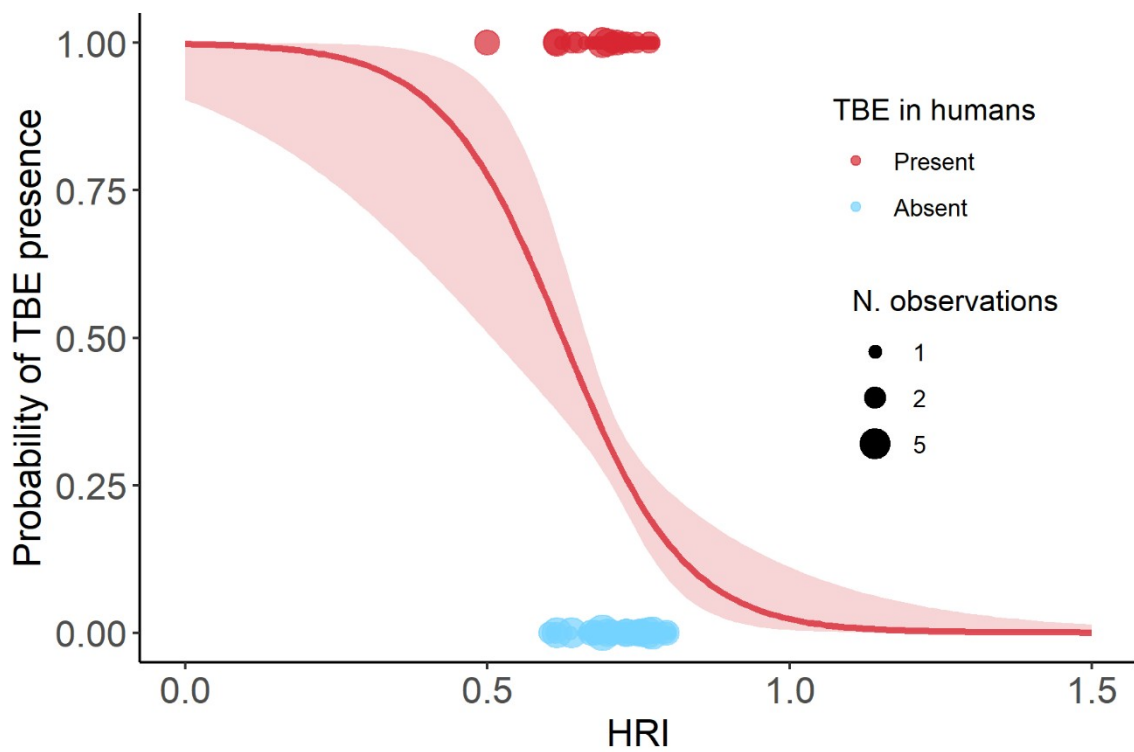
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273 *Figure 4) Estimated probability of TBE presence in the Trento and Belluno provinces*

274 *(Italy) based on HRI. Dots: Observed TBE presence (red) and absence (blue). Line: model*

275 *prediction. Shaded bands: 95% confidence interval.*

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Discussion

Tick-borne encephalitis (TBE) has become a growing public health concern in Europe, with an increasing number of reported human cases, despite the availability of a safe vaccine, and new natural foci of viral circulation appearing in previously non endemic areas.

The study of the relationship between biodiversity and disease risk in Europe is challenging due to the lack of quantitative data on abundance and density of wildlife species. We overcame this limit by using a newly developed indicator, the habitat richness index (HRI), to predict the probability of occurrence of human TBE cases at different spatial resolutions. Our results suggested that, at European scale, intermediate HRI maximizes TBE risk, which decreases at extreme (low and high) HRI values. This can be explained by the fact that European NUTS-2 and NUTS-3 regions included in the European-scale analysis are characterized by a great variety of habitat types, including habitats that are unsuitable for vector and host occurrence (compare Figure 1b and Figure 3b).

These findings were validated also at local scale, despite the narrower HRI range, where high TBE risk corresponds to areas with intermediate HRI. At the local scale, we found high TBE risk also at low HRI values. This result likely depends on the areas included at local-scale analysis, which feature habitat types that are generally suitable for ticks and host presence, as opposed to those corresponding to low TBE levels at European scale.

To fully understand the ecological implications of our findings, they need to be discussed in the context of the complex ecological mechanisms that underpin the viral circulation in the environment. TBEV circulation in the enzootic cycle is restricted to suburban and natural settings, as the establishment of a TBEV hotspot depends on environmental and behavioral factors associated with the presence of vectors and key animal hosts [8,9,44,45]. In this study, we found a negative, although non-significant, correlation between HRI and the presence of three species of cervids. This result is not surprising as

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303   spatial behavior of deer species is conditioned not only by habitat and environmental

304   features, but also by other factors such as, for example, human hunting pressure.

305   *A. flavicollis* and *C. glareolus* are widespread common forest species at European level

306   although they differ in habitat selection and food diet composition. Our results confirmed

307   the tight connection between the probability of presence of these species, *A. flavicollis* and

308   *C. glareolus* (which are indeed the main reservoirs for TBEV), habitat richness, and, in

309   turn, the occurrence of human TBE cases. Specifically, the significant negative correlation

310   between HRI and *A. flavicollis* presence, found at the European scale, suggests a higher

311   chance to find *A. flavicollis* in medium to low-diversity habitats, given its tendency to

312   occupy mainly mature forested areas with little or no shrub vegetation diversity [46,47]. Its

313   low presence in highly diversified habitats may decrease TBE risk thereafter. The same

314   negative relationship with HRI has been found for *C. glareolus*, although not significant.

315   This is probably due to its widespread occurrence in European forestry habitats with

316   different levels of vegetation diversity [48]. Overall, our results suggest a lower probability

317   of occurrence of TBEV reservoirs and tick-amplification hosts (i.e., rodents and deer), and

318   therefore a lower probability of TBEV circulation, in regions with higher habitat richness.

319   As high habitat richness is also related to high species richness [27] we speculate that

320   richer host communities with higher relative abundance of non-competent species could

321   affect the role of *A. flavicollis* and other competent rodent species on tick infection

322   prevalence by diverging blood meals of infected vectors away from competent hosts, and

323   consequently reducing the natural hazard of TBEV circulation, in accordance with the

324   dilution effect hypothesis [20,32]. Moreover, habitat destruction and the fragmentation of

325   landscapes into small, isolated units are known to cause reduction or elimination of some

326   vertebrate species and therefore diversity [49,50]. Often, species that occupy high trophic

327   levels (i.e. predators) are the most sensitive to such habitat destruction. Loss of these

328   species, although generally non competent reservoirs for vector-borne zoonoses, may

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329 increase disease risk (i) via reduction of diverted blood meals from these incompetent

330 hosts and (ii) via the loss of a regulatory 'predator' effect on typically more reservoir-

331 competent hosts (Ostfeld et al., 2004; Levi et al., 2012). In fact, mesocarnivore predators

332 (such as, for example, red foxes and mustelids) or birds of prey are known to regulate the

333 density of small mammals [18,51,52].

334 So far, we have taken into consideration the ecological aspects that play a fundamental

335 role in the natural hazard of TBE viral circulation and discussed how they might be

336 affected by habitat and species richness. However, habitat richness might also have an

337 impact on human exposure to infected ticks. Indeed, *I. ricinus*, the principal vector of TBEV

338 in Europe, is mainly found in pastures, deciduous and mixed forests with abundant

339 undergrowth [53] but can also be found in public greenspaces within peri-urban

340 environments. Hence, human exposure to tick bites is enhanced when tourism or

341 occupational activities take place not only in the proximity of forests and easily accessible

342 areas with low vegetation, but also in urban or peri-urban recreational areas that feature

343 low to moderate habitat diversity [54,55].

344

345 CONCLUSIONS

346 To our knowledge, this is the first attempt at understanding the relationship between TBE

347 occurrence and habitat richness in Europe. Our findings suggest a broad, dampening

348 effect of habitat richness on potential disease burden. As a result, the ongoing human

349 driven reduction in biodiversity, coupled with climate change, could lead to more

350 widespread disease [56,57]. However, such a conclusion is not definite, and we are aware

351 of the limitations of this study. In fact, many crucial aspects of this interaction remain to be

352 explored, such as the role of low-quality hosts, the characteristics of host competence or

353 the vector preference. To have a thorough understanding of the TBE-diversity paradigm,

354 these aspects should be carefully investigated in *ad hoc* empirical analysis aimed at

355 assessing how species diversity and host community composition influences local TBEV

356 circulation.

357 In this study, we aimed to provide new evidence on the conditions (including direct or

358 indirect roles of biodiversity, wildlife and land use) that promote the emergence and spread

359 of TBE. Disentangling the relationship between habitat richness and TBE risk on an EU-

360 wide basis is important to consistently inform public health authorities and support their

361 prevention and control activities in areas where TBE viral circulation is more likely to occur.

362 Furthermore, this study could support community efforts, such as the recently approved

363 EU Nature Restoration Law, that are aimed at the conservation and protection of species

364 and ecosystems in the European Union.

365

366 **Statements**

367 **Contributors:** Francesca Dagostin: Conceptualization, Methodology, Data Curation,

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369 Methodology, Writing - Review & Editing. Giovanni Marini: Conceptualization,

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376 Annapaola Rizzoli: Conceptualization, Methodology, Supervision, Writing - Review &

377 Editing.

378 **Declaration of interest:** We declare no competing interests.

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379 **Data sharing:** The data that support the findings of this study are available from ECDC,

380 Azienda Provinciale per i Servizi Sanitari Provincia Autonoma di Trento (APSS) and Unità

381 Locale Socio Sanitaria Dolomiti (ULSS N.1 Dolomiti). Restrictions apply to the availability

382 of these data, which were used under license for the current study, and so are not publicly

383 available. Code sources are available from the corresponding author upon reasonable

384 request.

385 **Disclaimer:** The views and opinions of the authors expressed herein do not necessarily

386 state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the

387 findings they report are not the responsibility of ECDC. ECDC is not responsible for

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389 correctness of the data and for data management, data merging and data collation after

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391 data.

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