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Exposure to tick-borne encephalitis virus among nature management workers in the Netherlands

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ABSTRACT

Tick-borne encephalitis virus (TBEV) has only recently been detected in the Netherlands. With still few autochthonous tick-borne encephalitis (TBE) patients, human exposure to TBEV is expected to be very low among the general population. We aimed to assess the exposure to TBEV among persons with an occupationally high risk of tick bites in the Netherlands.

In our cross-sectional serological survey, employees and volunteers of nature management organizations provided a single blood sample and completed an online questionnaire in 2017. The sera were screened in the anti-TBEV IgG Enzyme-Linked Immunosorbent Assay (ELISA), after which a TBEV-specific virus neutralization test (VNT) was applied to confirm positive ELISA outcomes.

Ten sera tested positive for IgG antibodies in the TBEV ELISA, among 556 participants who did not report vaccination against TBEV. Through confirmation in VNT, TBEV-specific IgG antibodies were detected among 0.5% (3/556, 95%CI 0.1%–1.6%). During the five years prior to the questionnaire, 87% reported tick bites. Half of the participants considered that most of their tick bites (75% to 100%) had been acquired while being at work.

A very low seroprevalence of TBEV exposure was observed among these nature management workers, even though they report a six times higher exposure to tick bites, compared to our general population. Nonetheless, the emergence of TBEV in the Netherlands reaffirms the need for education and preventative measures against tick bites and tick-borne diseases.

1. Introduction

Tick-borne encephalitis virus (TBEV), a member of the Flaviviridae family, is mainly transmitted in Western and Central Europe through bites of Ixodes ricinus. Within its geographical range, the virus tends to occur patchily in local foci in which the virus circulates between vertebrate hosts and ticks (Süss, 2011; Lindquist and Vapalahti, 2008). Tick-borne encephalitis (TBE) poses a growing public health problem in Europe, due to geographical expansion of TBEV during the past decades (Beauté et al., 2018; ECDC, 2014). The incidence has been increasing in Europe, causing a high disease burden and costs for healthcare and society (Beauté et al., 2018; Bogovic and Strle, 2015; ECDC, 2014; Süss, 2011; Šmit and Postma, 2015). According to the European center for Disease Prevention and Control, 3 092 cases of tick-borne encephalitis (TBE) were confirmed in 2018 in EU/EEA countries (ECDC 2019). Infection with the European variant of TBEV often (70% - 98%) resolves without symptoms, or with only mild flu-like illness (Kaiser, 2008; Gustafson et al., 1992). Symptomatic infection of the central nervous system usually manifests as meningitis or meningoencephalitis, sometimes causing lasting sequelae, and sporadically death (Kaiser, 2008, 2012; Ruzek et al., 2010).

TBEV was thought to be absent in the Netherlands, until TBEV was detected in ticks collected in 2015 from National Park Sallandse Heuvelrug, located in the East of the Netherlands. The first patients with autochthonous TBE were diagnosed during the summer of 2016, soon after the Center for Infectious Disease Control at the RIVM (National Institute for Public Health and the Environment, the Netherlands) informed clinicians and microbiologists about the possibility of infection with TBEV in the Netherlands (Jahfari et al., 2016; de Graaf et al., 2016; Weststrate et al., 2017).

Between 2016 and 2019, the RIVM recorded seven patients with clinical TBE, who were most likely infected in the provinces of

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Gelderland, Utrecht and Overijssel, located in the center and East of the Netherlands (RIVM 2020; de Graaf et al. 2016; Geeraedts et al., 2019; Weststrate et al., 2017; Dekker et al., 2019; RIVM 2019). Little is known about human exposure to TBEV in the Netherlands. With still few autochthonous TBE patients, human exposure to TBEV is expected to be very low among the general population. However, individuals with an outdoor occupation, e.g. forestry workers, have an increased tick exposure and hence an elevated risk of tick-borne diseases (Cisak et al., 2012; De Keukeleire et al., 2018; Richard and Oppliger, 2015). Therefore, we initiated a cross-sectional serological survey among nature management workers, to assess the exposure to TBEV among persons with an occupationally high risk of tick bites in the Netherlands.

2. Methods

The protocol for this cross-sectional serological survey among nature management organizations in the Netherlands (number 16–767/D) was approved by the medical ethics committee of the University Medical Center in Utrecht, the Netherlands.

To increase the chance of detecting exposure to TBEV, we aimed to recruit at least 25% of all our participants from nature management organizations nearby Sallandse Heuvelrug, i.e. in the provinces of Gelderland, Overijssel or Utrecht. Due to this sampling strategy, the current survey may not be representative of all nature management workers in the Netherlands.

During the first quarter of 2017, we announced the study among nature management organizations all across the Netherlands. These organizations are acknowledged at the end of this report, for disseminating the announcement about the study to their employees and volunteers, mainly through their occupational health physicians. Participation was discouraged for people who were vaccinated against TBEV. Employees and volunteers who were interested in participation were invited to send an e-mail to the RIVM to request information. Between April and December 2017, 963 individuals were invited for participation through an e-mail with an information letter and a personalized link to the online questionnaire. The study questionnaire inquired about socio-demographic characteristics, general health, professional occupation and geographical areas of work. Vaccination history was assessed for TBEV, yellow fever virus and Japanese encephalitis virus, as well as self-reported hospital diagnoses for disease due to one of these flaviviruses. Travel history outside of the Netherlands was assessed for the preceding twelve months, and lifetime travel history to tropical destinations. A blood collection set was sent to participants who committed to submit a blood sample, with instructions to visit their nearest blood draw facility for a venepuncture. One serum tube (7 ml), plus written informed consent for study participation, was sent to our laboratory at the RIVM by regular mail.

2.1. Serology & statistical data analyses

The sera were screened at the RIVM for IgG antibodies using the anti-TBEV IgG Enzyme-Linked Immunosorbent Assay (ELISA) [TestLine Clinical Diagnostics, Czech Republic] according to the manufacturer's instruction. The ELISA test results were scored according to the index of positivity (IP) as negative (IP < 0.9), borderline (IP 0.9 to 1.1), or positive (IP > 1.1). Sera with positive ELISA test result were sent to the Department of Virology of the Medical University Vienna, Austria for confirmatory testing in their inhouse TBEV-specific virus neutralization test (VNT) with TBEV-Eu Neudoerfl strain, and performed according to Holzmann et al. (Holzmann et al., 1996; Holzmann, 2003). Positive ELISA outcomes were considered as confirmed when the VNT titer was 30 or higher.

Participants who reported TBEV vaccination in their questionnaire, were excluded from statistical analyses. Descriptive statistics were performed in SAS version 9.4 to investigate the data retrieved from the questionnaires and serological status for TBEV-specific IgG antibodies. Participants whose serum tested positive in the neutralization test were considered to have been exposed to TBEV. The prevalence of VNT confirmed TBEV-IgG antibodies in serum, was calculated with exact binomial 95% confidence intervals (95%CI).

3. Results

3.1. Characteristics of participants & tick bite exposure

The online questionnaire was completed by 674 (70%) out of 963 invited participants. A blood sample was submitted by 563 participants with completed questionnaires. Seven participants were excluded from statistical analyses as they reported having been vaccinated against TBEV. Table 1 shows the characteristics of 556 study participants with a blood sample and questionnaire data, who did not report TBEV vaccination. Participants' age ranged from 22 to 80, with a median of 60 years of age, and most participants were male (82%). Almost a third (29%) of participants reported having worked in more than one province. Occupational functions reported by more than 5% of the participants are listed in Table 1. More than half (55%) of the participants were voluntary workers, i.e. working unpaid for the nature management organizations. Other frequently reported occupational functions were forest ranger (24%), field worker (23%), forest worker (16%), site manager (16%), and nature conservationist (15%). The majority of participants (71%) reported tick bites during the 12 months before the study, and even more participants (87%) reported tick bites during the five years before the study. A third (36%) of the participants reported weekly to monthly tick bites during tick bite seasons. Half (49%) of the participants considered most of their tick bites (75% to 100%) related to work. The most frequently reported occupational activities with high tick bite exposure, were sitting on grass during work or break (reported by 50% of participants), inventory and monitoring activities (42%), maintenance (40%), tree pruning (38%), and working in heathland (36%). Yellow fever vaccination was reported by 82 participants (15%), and none recalled vaccination against Japanese encephalitis virus. Traveling abroad during the preceding 12 months was reported by 72% of participants, and over half (54%) of the participants had ever travelled to a tropical destination.

The 111 (16%) participants who did not submit a blood sample following completion of the questionnaire were on average 11.4 years younger (mean age 46.1) compared to the 563 participants with a blood sample (mean age 57.5, $p < 0.0001$ in pooled t-test). No differences between the participants with ($n = 563$) and without ($n = 111$) a blood sample were observed in proportions for gender, nor for tick bites during the 12 months or 5 years before the study.

3.2. TBEV seroprevalence

Ten sera tested positive for IgG antibodies in the TBEV ELISA, after which three were confirmed in VNT. This results in a TBEV-specific IgG antibody seroprevalence of 0.5% (95%CI 0.1% – 1.6%) among the 556 participants who did not report vaccination against TBEV. The outcome values of the ELISA and VNT assays of the ten ELISA positive participants are shown in Table 2, with reported vaccination history for yellow fever virus. The three VNT-confirmed participants reported travel to tropical destinations during their lifetime, and travel abroad during the preceding year, including countries where TBE is endemic. During the preceding year, one participant reported travel to Spain, Canada and Denmark; one participant reported travel to Hungary and Austria; one participant reported travel to Austria and Germany. These three VNT-confirmed participants had not ever been diagnosed with TBE or any other flaviviral disease, nor did they report hospitalization during the year before the study. They had worked in the provinces Overijssel, Gelderland, Flevoland and Limburg, during the year preceding to the study.

Table 1
Characteristics and IgG-positivity of 556 study participants with an occupationally high risk of tick bites in the Netherlands, 2017. Seven participants who reported TBEV vaccination were excluded from this analysis.

	Overall $N = 556$	% of 556	TBEV-ELISA IgG positive $N = 10$	TBEV-VNT positive $N = 3$
Socio-demographics & employment				
Gender				
Men	458	82.4%	7	2
Women	98	17.6%	3	1
Median age in years (min – max)	60	(22 - 80)		
Age groups				
20–30 years	24	4.3%	1	1
31–40 years	52	9.4%	2	2
41–50 years	74	13.3%	0	0
51–60 years	133	23.9%	4	0
61–70 years	195	35.1%	2	0
70> years	78	14.0%	1	0
Geographical area (province) of employment, past year*				
Gelderland	172	30.9%	1	1
Noord-Brabant	148	26.6%	4	0
Limburg	80	14.4%	1	1
Overijssel	79	14.2%	2	2
Noord-Holland	71	12.8%	1	0
Utrecht	66	11.9%	1	0
Drenthe	65	11.7%	0	0
Friesland	53	9.5%	1	0
Flevoland	51	9.2%	1	1
Zuid-Holland	48	8.6%	0	0
Groningen	39	7.0%	1	0
Zeeland	21	3.8%	0	0
Occupational functions reported by more than 5% of participants*				
Volunteer worker	305	54.9%	6	1
Forest ranger	134	24.1%	3	2
Field worker	126	22.7%	2	1
Forest worker	91	16.4%	2	1
Site manager	86	15.5%	1	0
Nature conservationist	85	15.3%	1	1
Landscape manager	62	11.2%	2	0
Supervisor	62	11.2%	1	0
Researcher	43	7.7%	0	0
Arborist	33	5.9%	1	1
Hunter	28	5.0%	0	0
Tick bite exposure & occupational activities				
Number of tick bites, past year				
None	161	29.0%	4	1
1–3	219	39.4%	2	0
4–10	122	21.9%	3	1
11–50	45	8.1%	0	0
50>	8	1.4%	1	1
Missing	1	0.2%	0	0
Frequency of tick bites during tick bite season, past 5 years				
At least weekly	58	10.4%	1	1
Monthly	140	25.2%	4	1
Annually	144	25.9%	0	0
Less frequently	142	25.5%	5	1
Never	71	12.8%	0	0
Missing	1	0.2%	0	0
Estimated proportion of tick bites that were acquired occupationally				
0% to 25%	92	16.6%	0	0
25% to 75%	66	11.9%	0	0
75% to 100%	270	48.6%	6	2
Don't know	128	23.0%	4	1
Top 5 occupational activities with highest frequency of tick bites, past year*				
Sitting on grass during work / break	279	50.2%	6	2
Inventory and monitoring activities	234	42.1%	3	2
Maintenance activities	223	40.1%	5	0
Tree pruning & maintenance	212	38.1%	4	0
Working in heathland	202	36.3%	3	2
Travel & flavivirus vaccinations				
Travel*				
Outside of the Netherlands, past year	401	72.1%	8	3
To tropical destinations, lifetime	298	53.6%	8	2
Flavivirus vaccinations, other than TBEV*				
Yellow fever vaccination	82	14.8%	4	1
Japanese encephalitis vaccination	0	0.0%	0	0

n.a. = not available.
* percentages add up to more than 100%, because categories are not mutually exclusive.

Table 2
Assay values and reported vaccination history of participants who tested positive for IgG antibodies in the TBEV ELISA. Seven participants who reported TBEV vaccination were excluded.

Participant number	TBEV ELISA value	VNT titers	Time since yellow fever vaccination
1	6.1	120	5 years ago
2	3.0	30	–
3	1.3	30	–
4	3.6	Negative	–
5	3.0	Negative	Vaccinated, unknown year
6	2.8	Negative	–
7	2.6	Negative	–
8	2.6	Negative	–
9	2.4	Negative	19 years & 28 years ago
10	2.1	Negative	> 30 years ago

4. Discussion

For the first time, exposure to TBEV among people across the Netherlands has been assessed. Through this cross-sectional serological survey, we detected TBEV-specific IgG antibodies among 0.5% of our study participants who worked in nature management in the Netherlands in 2017. This seroprevalence is consistent with the low number of registered clinical TBE patients in the Netherlands. Our seroprevalence is lower than the rates reported from comparable studies regarding occupationally high tick bite exposure in neighbouring countries. Correspondingly, the numbers of registered numbers of patients with clinical TBE in those regions are higher. In the German state of North Rhine-Westphalia, which borders the South East of the Netherlands, antibodies against TBEV were detected by VNT, following a screening ELISA, in 3.4% of 722 forestry workers in 2011–2013 (Jurke et al., 2015). North Rhine-Westphalia is not considered a risk area with fourteen registered patients with clinical TBE during the past five years (mean annual incidence below 0.5 per 100,000 inhabitants) (Koch-Institut, 2020). In northeastern France, antibodies against TBEV were detected by ELISA in 2.3% of 2941 forest workers in 2003 (Rigaud et al., 2016; Thorin et al., 2008). This is consistent with the low and stable incidence of clinical TBE in France during the same years, as about one to nine TBE patients have been registered per year between 1968 and 2003, and mainly confined to Eastern France (Hansmann et al., 2006). Seroprevalence studies in other regions where TBE has recently been detected, e.g. the South of England and Denmark, could be valuable for public-health assessment and awareness of clinicians. These would also enable further comparison of epidemiological features and case finding between regions (Beauté et al., 2018; Holding et al., 2020; Fomsgaard et al., 2009).

Anticipating that TBEV occurs rarely in the Netherlands, we aimed to increase the sensitivity of detecting TBEV exposure in this survey by targeting people with a relatively high risk of tick bites. Indeed, our participants reported a very high exposure to tick bites, exceeding the tick bite exposure among the general population by six-fold. During the five years prior to the questionnaire, 87% of our participants reported tick bites, whereas 13% of a representative sample of inhabitants of the Netherlands reported tick bites during the 5 years prior to 2007 (Hofhuis et al., 2015). The prevalence of exposure to TBEV among our general population is yet unknown, although it is expected to be even lower than in our study population. Nonetheless, each year more than a million tick bites occur among the population of the Netherlands (Hofhuis et al., 2016, 2015). We expect that TBE case finding is impaired by low awareness of this recently emerged disease among our clinicians and microbiologists. Further improvement of such awareness would benefit the diagnosis of patients with clinical TBE and would improve the monitoring of trends in the incidence and geographical spread of clinical TBE in the Netherlands. Roe deer blood samples obtained in 2017 indicate a more widespread exposure to TBEV than in the provinces where TBE patients have been observed. A map of the spread of TBEV in the Netherlands was recently published by the RIVM, using available information on TBEV in wild animals, ticks and the most probable location of infection for patients who were diagnosed with TBE (RIVM, 2020). Further investigation of the geographical spread and ecology of TBEV in ticks and animals is ongoing (Jahfari et al., 2016; Rijks et al., 2019).

Using serology to detect the generally prolonged persistence of TBEV-specific IgG antibodies in serum, we have observed that three of our participants have likely been in contact with TBEV at some point in their lives. The clinical expression of TBEV infection cannot be inferred from these serological outcomes. Consistent with the general experience that the majority of TBEV infections resolve without severe symptoms (Amicizia et al., 2013; Bogovic and Strle, 2015; Süss, 2011), the three VNT-confirmed participants did not report recent hospitalization nor did they report ever having been diagnosed with TBE. Seven participants who reported TBEV vaccination were excluded from statistical analyses as serology does not distinguish between TBEV-specific IgG antibodies acquired by vaccination, or by exposure to the virus. However, people may not always recall their vaccination status correctly, and we could not rule out that the participants, who did not report TBEV vaccination, were truly unvaccinated. The mode of TBEV transmission can also not be inferred from these serological outcomes, so it is not known whether TBEV exposure occurred during occupational or leisure activities, nor whether TBEV exposure occurred in a certain province of the Netherlands or abroad. Travel to TBE endemic countries was reported by two VNT-confirmed participants. Statistical analysis on possible risk factors for TBEV exposure, such as geographical area of employment, was not feasible due to the low number of VNT-confirmed participants.

Due to similarities in antigenic determinants between flaviviruses such as TBEV, yellow fever, dengue, Zika, West Nile, Japanese encephalitis and Powassan viruses, antibody cross-reactivity could result in false-positive results in serological assays other than neutralization tests (e.g. ELISA) (Bradt et al., 2019). Therefore TBEV-ELISA positives were confirmed by VNT, and our questionnaire inquired about exposure to, and vaccination against yellow fever virus. We did not observe an influence of yellow fever vaccination induced antibodies on the measured TBEV responses. Among 82 yellow fever-vaccinated participants, we found few ($n = 4$) positive TBEV-ELISA outcomes. One of the four TBEV-ELISA positive outcomes among yellow fever-vaccinated participants were confirmed in TBEV-VNT confirmation (subject #1 in Table 2). This is in line with what has been described by Bradt et al. They tested the influence of yellow fever vaccination on TBEV-VNT outcomes, but found no cross reactivity in the TBEV-VNT (Bradt et al., 2019). The emergence of TBEV in the Netherlands provides another reason, in addition to Lyme borreliosis, for preventative measures against tick bites and tick-borne diseases. In our online questionnaire, half of the participants reported that they considered the majority of their tick bites to be occupationally acquired. The occupational setting with high exposure to ticks requires continuous education, tailored to nature management workers, about prevention of tick bites and tick-borne diseases (protective clothing e.g., impregnated with insecticides, skin insect repellents, examination of body and clothes at the end and during every working day, rapid detection and - albeit mainly successful for tick borne infections other than TBEV- immediate removal of attached ticks from the skin). Widely available vaccines for TBEV provide a safe, reliable and efficacious protection. Neither the very low incidence of clinical TBE in the Netherlands as a whole, nor the incidence within TBEV affected provinces, meet the WHO criteria for recommendation of TBEV vaccination for the general population (disease incidence of >5 TBE patients per 100,000 population per year (Who, 2011)). However, adherent to the precautionary principles of occupational health care, some nature management organizations recommend vaccination to employees and volunteers who work in or nearby areas where TBEV has been detected (Stigas, 2020; VBNE, 2019). To date, no data are collected on TBEV vaccination coverage in the Netherlands.

Author statement credit roles

The study concept and design was developed by AH, JHJR, FSMR, CCvdW.

AH and EF obtained funding. Data collection was performed by AH and OEvdB.

Laboratory testing was performed and interpreted by NHC and JHJR.

OEvdB, AH, and JHJR analyzed and interpreted the data.

OEvdB and AH drafted the manuscript.

The study was supervised by AH and EF.

All authors were involved in critical revision of the manuscript and all authors read and approved the final manuscript.

Declarations of Competing Interest

None.

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