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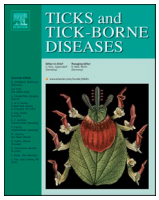

Review Article

Systematic review on the non-vectorial transmission of *Tick-borne encephalitis virus* (TBEv)

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ABSTRACT

Tick-borne encephalitis (TBE) is an infection caused by the *Tick-borne encephalitis virus* (TBEv) and it is common in Europe. The virus is predominantly transmitted by ticks, but other non-vectorial modes of transmission are possible. This systematic review synthesises the epidemiological impact of non-vectorial modes of TBEv transmission in Europe. 41 studies were included comprising of 1308 TBE cases. Alimentary (36 studies), handling infected material (3 studies), blood-borne (1 study), solid organ transplant (1 study) were identified as potential routes of TBEv transmission; however, no evidence of vertical transmission from mother to offspring was reported (2 studies). Consumption of unpasteurised milk/milk products was the most common vehicle of transmission and significantly increased the risk of TBE by three-fold (pooled RR 3.05, 95% CI 1.53 to 6.11; 4 studies). This review also confirms handling infected material, blood-borne and solid organ transplant as potential routes of TBEv transmission. It is important to tracing back to find the vehicle of the viral infection and to promote vaccination as it remains a mainstay for the prevention of TBE.

1. Introduction

Tick-borne encephalitis (TBE) is one of the most frequently reported tick-borne diseases in Europe. *Tick-borne encephalitis virus* (TBEv) is a member of the genus *Flavivirus*, in the family *Flaviviridae* (Lindquist and Vapalahti, 2008). There are three subtypes of TBEv: European, Siberian, and Far Eastern (Lindquist and Vapalahti, 2008). Two additional TBEv subtypes (Baikalian and Himalayan) have recently been proposed (Dai et al., 2018; Tkachev et al., 2020). The European subtype is prevalent in parts of western, northern, central, and eastern parts of Europe. Between 10,000 and 12,000 cases of TBE are reported each year (World Health Organization, 2011), although this is likely an underestimation of the actual number of infection as a large proportion of the infections remain asymptomatic (Bogovic and Strle, 2015). There were 3,246 confirmed cases of TBE reported from EU/EEA countries in 2019, equating to 0.7 cases per 100,000 population, a slight increase compared with the three previous years (European Centre for Disease Prevention and Control, 2021b). The rise in the number of reported cases in recent years is likely driven by several factors including improved diagnostic tests, increased disease awareness, spending more time outdoors, as well as temperature rises (Sumilo et al., 2007; Zavadska et al., 2013).

The main transmission mode for TBEv is via tick bites: the European subtype is primarily transmitted by *Ixodes ricinus*, whilst the Siberian and Far Eastern subtypes are mainly transmitted by *Ixodes persulcatus* (World Health Organization, 2011). Transmission can also occur following consumption of unpasteurised milk and milk products from infected cows, goats, and sheep (Rieger et al., 1998; Ličková et al., 2022; Buczek et al., 2022). When an animal has been bitten by an infected tick, the virus can be secreted at low concentrations in milk during the viremic phase, and thus products made of unpasteurised milk can be infectious (Labuda et al., 2002; Zeman et al., 2004). Other non-vectorial modes of TBEv transmission could be possible. To date, no systematic reviews have been conducted addressing non-vectorial transmission of TBEv. Therefore, we have conducted a systematic review to collect and synthesize information on different modes of non-vectorial TBEv transmission in Europe, discuss the epidemiological impact and

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potential prevention and mitigation measures that may be implemented.

2. Methods

This systematic review was conducted and reported adhering to the JBI methodology for systematic reviews (Aromataris and Munn, 2020) and the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) framework (Moher et al., 2009; Page et al., 2021), respectively. A protocol for the review (Supplement S1) was developed in April, 2021.

2.1. Inclusion criteria

We included all epidemiological studies on human cases of TBE from non-vectorial modes of transmission, including but not limited to foodborne transmission, direct transmission (including sexual, materno-fetal and breastfeeding transmission), transmission of the virus in a laboratory while handling infected material, blood-borne and organ-borne transmission. A case of TBE was defined as empirically reported within the included studies. Reviews, letters, and opinion pieces were excluded. We limited the search to the 27 member countries of the EU, Iceland, Norway, Switzerland, and the UK (Supplement S2) and excluded EU overseas territories.

2.2. Search strategy and study selection

Peer reviewed and grey literature were identified through comprehensive electronic searches of Medline, EMBASE, and CAB Abstracts (from inception to 28th April 2021) (Supplement S3). We also identified further relevant studies from scanning reference lists of included studies and previous reviews. We screened and included studies irrespective of language. We piloted title and abstract screening for 500 hits independently by two reviewers, where any discrepancies were resolved with a third reviewer. The percentage of agreement between the reviewers was over 90%, so the remaining titles and abstracts were screened by one reviewer. The full texts of the potentially eligible studies and studies which did not have abstracts available, were sourced and screened independently by two reviewers, with disagreements resolved with a third reviewer.

2.3. Data extraction and critical appraisal

Data extraction and critical appraisal of the methodological quality of the included studies were performed independently by two reviewers for 25% of the included studies, using standardized data extraction and JBI critical appraisal (https://jbi.global/critical-appraisal-tools). Negligible discrepancies were seen between the reviewers; therefore, only one reviewer conducted the extraction and critical appraisal of the remaining studies. The critical appraisal tool used was based on the data that could be extracted from the study (individual cases of TBE [case report tool], aggregate cases of TBE [case series tool], or comparative data of cases with TBE and controls without TBE [analytical cross-sectional studies tool]), since the study design did not directly relate to the data being extracted. Where detailed data were reported for multiple cases within a study, we used the first case as the basis for the critical appraisal assessment. Each question was assigned either ‘yes’, ‘no’, ‘unclear’ or ‘not applicable’ (NA). A high quality was given where all questions were answered as ‘yes’. A moderate score was given where the answers were either ‘yes’ or ‘unclear’. A low score was given where at least one answer was ‘no’. Answers assigned ‘not applicable’ were not included for assigning the score.

2.4. Data synthesis

The characteristics of the included studies are presented in tabular form detailing the mode of transmission, study design, geographical location of the study, sample size, characteristics of the cases considered, number exposed, setting, context, and main findings of the studies. Initially we used a narrative synthesis approach with content analysis to systematically describe and summarise the included studies categorized by the mode of transmission, geographical location of the study and decade of data collected to identify patterns in the data. For comparative studies of alimentary transmission, we conducted a random effects meta-analysis to quantify the magnitude of the association and expressed the results as relative risks (RR) with 95% confidence intervals (CI). Estimates adjusted for confounders or matched designs were used in preference to crude estimates. Heterogeneity was quantified using I^2 and explored using sensitivity analysis, where we excluded studies which had severe outlier results. Due to insufficient studies, we were unable to conduct planned subgroup analyses or publication bias assessment.

3. Results

3.1. Study selection

The searches identified a total of 7246 results, of which 158 were identified to be potentially eligible for full text screening. Of these, we included 41 studies (Aendekerk et al., 1996; Avšič-Županc et al., 1995; Balogh et al., 2010; Bodemann, 1977; Brockmann et al., 2018; Bušová et al., 2018; Caini et al., 2012; Chitimia-Dobler et al., 2021; Dive et al., 2020; Dorko et al., 2018, 2014; Gresiková and Sekeyová, 1976; Holzmann et al., 2009; Hudopisk et al., 2013; Ilic et al., 2020; Jezyna et al., 1976; Kerlik et al., 2018; Knežević et al., 2019; Kohl et al., 1989, 1996; Krbková et al., 2015; Kříž et al., 2009; Król et al., 2019; Labuda et al., 2002; Lindquist and Vapalahti, 2008; Markovinovic et al., 2016; Matuszczyk et al., 1997; Nicolini et al., 2011; Pazdiora et al., 2008; Pazdiora P, 1994; Rieger et al., 1998; Sixl et al., 1989; Szeles, 2008; Wahlberg et al., 1989; Zaludko et al., 1994; Zavadska et al., 2018; Zoldi et al., 2013; Donchenko et al., 2005; Pazdiora et al., 2012; Juceviciene et al., 2002; Lipowski et al., 2017), excluded 110 studies and 7 studies could not be retrieved (Fig. 1, Supplement S4). Eleven papers required translation into English from German (n=2), Czech (n=2), Polish (n=2), Hungarian (n=2), Slovakian (n=2) and Croatian (n=1).

The majority of studies investigated non-vectorial transmission of TBEv in single outbreaks (n=17, (Balogh et al., 2010; Brockmann et al., 2018; Caini et al., 2012; Chitimia-Dobler et al., 2021; Holzmann et al., 2009; Hudopisk et al., 2013; Jezyna et al., 1976; Knežević et al., 2019; Kohl et al., 1989, 1996; Król et al., 2019; Markovinovic et al., 2016; Matuszczyk et al., 1997; Pazdiora P, 1994; Sixl et al., 1989; Szeles, 2008; Donchenko et al., 2005)), with eight of these conducting an outbreak investigation (Brockmann et al., 2018; Caini et al., 2012; Chitimia-Dobler et al., 2021; Holzmann et al., 2009; Jezyna et al., 1976; Matuszczyk et al., 1997; Pazdiora, 1994; Szeles, 2008). Seven studies investigated non-vectorial transmission of TBEv in multiple outbreaks (Donchenko et al., 2005; Dorko et al., 2018, 2014; Kerlik et al., 2018; Labuda et al., 2002; Pazdiora et al., 2012; Zaludko et al., 1994); with one of these studies reporting both the results of a single and multiple outbreaks (Donchenko et al., 2005). A case report design was used in six studies (Aendekerk et al., 1996; Avšič-Županc et al., 1995; Camprubi et al., 2020; Dive et al., 2020; Nicolini et al., 2011; Lipowski et al., 2017) and a case series design was used in a further seven studies (Bodemann, 1977; Krbková et al., 2015; Kříž et al., 2009; Pazdiora et al., 2008; Wahlberg et al., 1989; Zavadska et al., 2018; Zoldi et al., 2013). The remaining five studies used a comparative design (Bušová et al., 2018; Gresiková and Sekeyová, 1976; Ilic et al., 2020; Juceviciene et al., 2002; Rieger et al., 1998), with one study reporting the results from a cross-sectional study and case-control study (Rieger et al., 1998).

Most of TBE patients became infected in Slovakia (10 studies) and Czechia (7 studies), then in Germany (4 studies), Hungary (4 studies), Croatia (3 studies), Poland (4 studies), Slovenia (3 studies), Austria (2 studies), Estonia (2 studies), Finland (1 study), Italy (1 study), Lithuania (1 study) and Sweden (1 study). One study (Dive et al., 2020) included

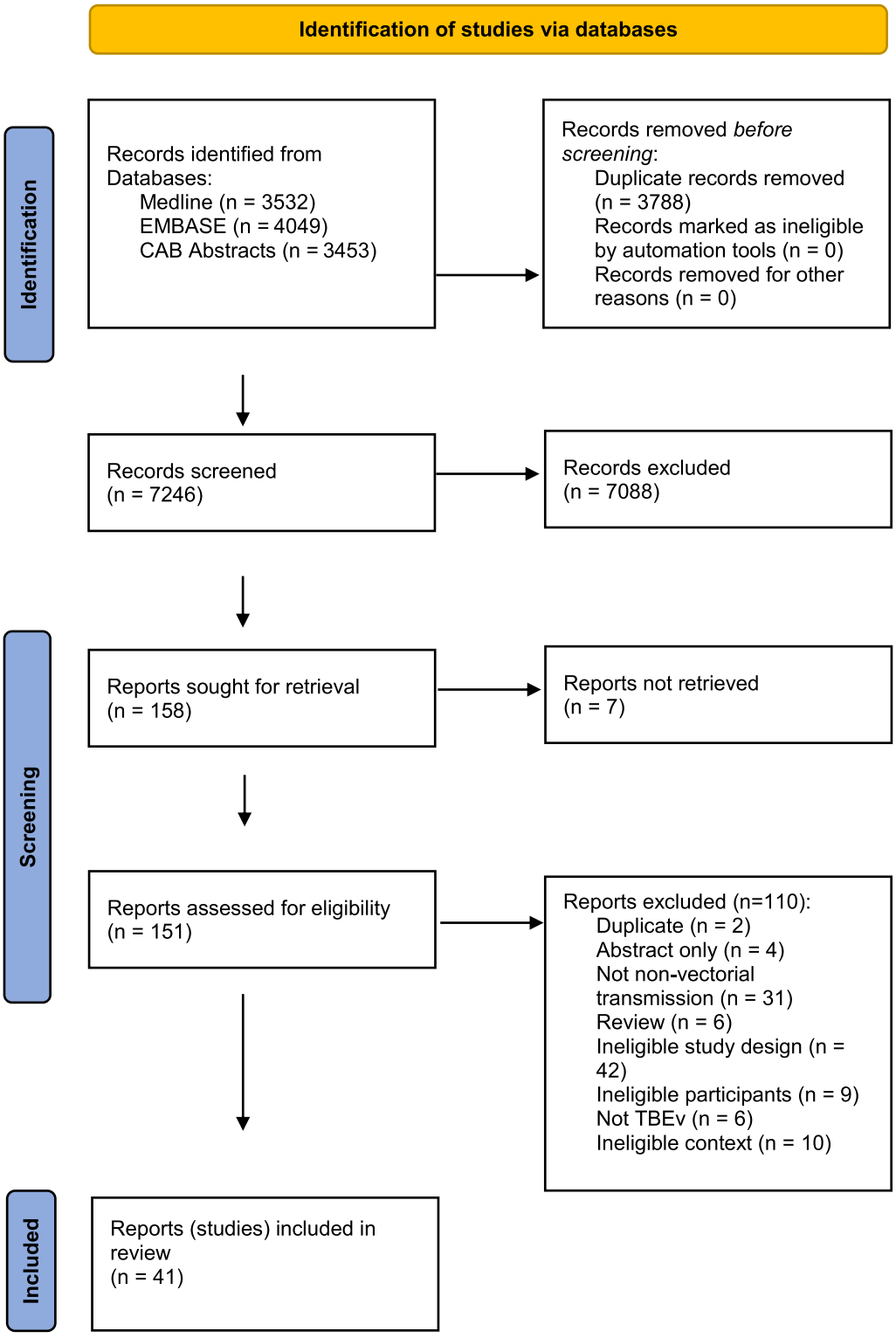

Fig. 1. PRISMA Flow chart of included studies.

two countries (Czechia and Sweden), therefore the total number of studies is 41. The diagnosis of TBE was based on either the detection of antibodies in serum only (Aendekerk et al., 1996; Avšič-Županc et al., 1995; Balogh et al., 2010; Bušová et al., 2018; Chitimia-Dobler et al., 2021; Dorko et al., 2014; Gresiková and Sekeyová, 1976; Hudopisk et al., 2013; Jezyna et al., 1976; Juceviciene et al., 2002; Knežević et al., 2019; Kohl et al., 1989, 1996; Kříž et al., 2009; Pazdiora P, 1994; Rieger et al., 1998; Szeles, 2008; Wahlberg et al., 1989) or in serum and cerebrospinal fluid (CSF) (Bodemann, 1977; Brockmann et al., 2018; Caini et al., 2012; Camprubi et al., 2020; Dive et al., 2020; Dorko et al., 2018; Holzmann et al., 2009; Ilic et al., 2020; Kerlik et al., 2018; Król et al., 2019; Markovinovic et al., 2016; Matuszczyk et al., 1997; Nicolini et al., 2011; Pazdiora et al., 2012; Zaludko et al., 1994; Zavadska et al., 2018). Three papers also reported the direct search of the virus in the umbilical cord blood, urine, amniotic fluid (Dive et al., 2020), in the serum (Avšič-Županc et al., 1995; Hudopisk et al., 2013), or in the brain

or CSF (Lipowski et al., 2017).The remaining five studies did not report information to ascertain the approach taken to diagnose TBE (Donchenko et al., 2005; Krbková et al., 2015; Labuda et al., 2002; Pazdiora et al., 2008; Sixl et al., 1989; Zoldi et al., 2013). The characteristics of included studies highlighting the mode of transmission, the potential source of infection or vehicle of infection, the setting of infection, the number of infected people and the vaccination status for each study are reported in Table 1.

3.2. Alimentary transmission: main findings

Most included studies assessed alimentary infection as the mode of transmission of TBEv (n=36, Table 1. The vehicle of infection was consumption of unpasteurized milk and milk products (from here on referred to as milk products) (Table 2). The infection was contracted in the same country as the cases resided for all studies, except for one case where the person was infected in Estonia before travelling back to Spain (Camprubi et al., 2020) (Table 3). Details on study design, number of cases, age and sex, month of exposure to the vehicle of alimentary infection and hospitalization details are reported in Table 3. In the studies reporting vaccination status of the cases, all the participants in the studies were unvaccinated except in two studies (Chitimia-Dobler et al., 2021; Hudopisk et al., 2013). In one study, one TBE case was vaccinated; however, this case received their last vaccine shot 15 years prior to onset of symptoms (Chitimia-Dobler et al., 2021). In the other study, one asymptomatic case had their booster dose two years before exposure to the virus (Hudopisk et al., 2013).

Seven studies assessed the association between exposure to alimentary vehicle of infection and TBE (Bušová et al., 2018; Caini et al., 2012; Ilic et al., 2020; Juceviciene et al., 2002; Rieger et al., 1998; Szeles, 2008; Gresiková and Sekeyová, 1976). A meta-analysis of five studies (Caini et al., 2012; Ilic et al., 2020; Juceviciene et al., 2002; Rieger et al., 1998; Szeles, 2008) found consuming unpasteurized milk products did not significantly increase the risk of having TBE (RR 27.82, 95% CI 0.77 to 1008.83, I^2=98%; Fig. 2). A sensitivity analysis excluding one study (Szeles, 2008) due to outlier results, found a significant three-fold increase in the risk of TBE associated with consumption of unpasteurised milk products (RR 3.05, 95% CI 1.53 to 6.11; I^2=34%; Fig. 2). Similar findings were also seen in two further studies which could not be included in the meta-analysis due to the type of effect measure reported (Bušová et al., 2018) or due to providing very limited results (Gresiková and Sekeyová, 1976).

Eleven studies reported the number of cases of TBE via alimentary transmission over time (Donchenko et al., 2005; Dorko et al., 2018, 2014; Kerlik et al., 2018; Krbková et al., 2015; Kříž et al., 2009; Labuda et al., 2002; Pazdiora et al., 2008; Sixl et al., 1989; Zavadska et al., 2018; Zoldi et al., 2013). Details of these studies are reported in Supplement S5. The characteristics of the 16 remaining studies which presented data for individual cases are presented in Table 3.

3.3. Handling infected materials in a laboratory setting: main findings

Three studies (Table 1) assessed infection via the handling of infected materials in a laboratory setting as the mode of transmission of TBEv (Avšič-Županc et al., 1995; Bodemann, 1977; Wahlberg et al., 1989). Six people were exposed to TBEv via laboratory manipulations, all of which developed TBE, with diagnosis being made using serology. Details on study design, number of cases, age and sex, month of exposure to the vehicle or source of infection and hospitalization details are reported in Table 3. In one study, the unvaccinated patient worked as a microbiologist, where transmission occurred via aerosol probably during the centrifugation of TBEv infected mouse brain suspensions performed outside of the safety cabinet (Avšič-Županc et al., 1995). The cases from the remaining two studies were employed as laboratorists (3 cases with no information on vaccination status (Wahlberg et al., 1989) and 2 cases unvaccinated (Bodemann, 1977)) who were involved, for example, in the production of the TBEv antigen and the transfer of infectious material to mice (Bodemann, 1977).

3.4. Vertical transmission: main findings

Two studies (Table 1) assessed vertical transmission as the potential mode of transmission of TBEv (Dive et al., 2020; Ilic et al., 2020). The first study focused on two cases of pregnant women who were hospitalized with TBEv infection (Dive et al., 2020). One case was a 30-year--old pregnant woman who resided in Germany but became infected following a trip to Czechia. The child was born 21 weeks after symptom onset. The second case was a 40-year-old woman with twin pregnancy who became infected in her home country of Sweden. The twins were born seven weeks after symptom onset. In both cases it was not specified whether the children were born prematurely. Neither of the women was vaccinated against TBE. None of the children developed TBE; however, IgG antibodies were present in the umbilical cord blood of all children, and IgG antibodies in their blood declined until they became non-detectable at approximately 9-15 months of age; thus materno-fetal transmission of TBEv was excluded.

The second study included a case where the potential for vertical transmission via breastfeeding was assessed (Ilic et al., 2020). An outbreak of TBE occurred on a farm in Croatia in five people who consumed unpasteurized goat milk, including an unvaccinated woman who was breastfeeding. The serological test for TBE in the infant (age unknown) was negative, and although there was no mention whether the breastmilk was tested, there was no vertical transmission of TBEv through breastfeeding.

3.5. Blood transfusion: main findings

One study (Table 1) assessed blood transfusion as the mode of transmission of TBEv (Wahlberg et al., 1989). The study reported single cases of TBE from 1959-1987 in Finland. Two cases of TBE (one male, one female) underwent blood transfusions in hospital (year unknown). TBE was confirmed in both patients; however, only one of the cases demonstrated biphasic symptoms, with the other demonstrating only phase 2 symptoms. No information on the recovery following TBEv infection nor further detail in how they determined that blood transfusion was the mode of transmission were reported.

3.6. Solid organ transplant transmission: main findings

One study (Table 1) assessed solid organ transplant as the mode of transmission of TBEv (Lipowski et al., 2017) in Poland. This study reported the transmission of the virus through transplanted organs (liver and kidneys) from a single infected donor (male) to three recipients (male). The recipients became ill 17–49 days after transplantation and died few days later in hospital. TBEv infection was confirmed after death in all four people by NGS and RT-PCR.

3.7. Other modes of transmission

No studies were identified which assessed other potential modes of transmission of TBEv, for example, sexual transmission.

3.8. Critical appraisal of included studies

Of the 12 studies assessed for methodological quality using the case report tool, six studies scored as high quality (Avšič-Županc et al., 1995; Camprubi et al., 2020; Hudopisk et al., 2013; Król et al., 2019; Markovinovic et al., 2016; Lipowski et al., 2017), three studies had a moderate quality (Bodemann, 1977; Dive et al., 2020; Holzmann et al., 2009), and the remaining three studies had a low score (Aendekerk et al., 1996; Bodemann, 1977; Nicolini et al., 2011). Of the 26 studies assessed using the case series tool (Balogh et al., 2010; Brockmann et al., 2018; Caini

Table 1
Characteristics of included studies (ordered by country where acquired infection with TBEv).

Author, year	Mode of transmission	Potential source of infection or vehicle of infection	Setting of infection	Number of people with confirmed TBE*	Vaccination status of people with confirmed TBE
Austria					
(Holzmann et al., 2009)	Alimentary	Unpasteurized mixture of cow and goat milk	Not reported	6	Unvaccinated
(Sixl et al., 1989)	Alimentary	Unpasteurized goat milk	Not reported	2	Not reported
Croatia					
(Ilic et al., 2020)	Alimentary / Vertical transmission	Unpasteurized goat milk / breast feeding	Goat farm	5 / 0	Unvaccinated
(Knežević et al., 2019)	Alimentary	Unpasteurized goat milk or milk products	Small family farm	5	Unvaccinated
(Markovinovic et al., 2016)	Alimentary	Unpasteurized goat milk or milk products	Family goat farm	5	Unvaccinated
Czechia					
(Aendekerk et al., 1996)	Alimentary	Unpasteurized goat milk	Not reported	1	Not reported
(Krbková et al., 2015)	Alimentary	Unpasteurized goat milk or milk products	Not reported	4	Not reported
(Kříž et al., 2009)	Alimentary	Unpasteurized goat or cow milk, or sheep cheese	Bought or consumed products from animal breeders	64	Unvaccinated
(Pazdiora, 1994)	Alimentary	Unpasteurized goat milk yogurt	Family home	3	Unvaccinated
(Pazdiora et al., 2008)	Alimentary	Unpasteurized goat milk	Not reported	40	Not reported
(Pazdiora et al., 2012)	Alimentary	Unpasteurized goat milk	Not reported	11	Not reported
Czechia and Sweden					
(Dive et al., 2020)	Vertical transmission	Materno-fetal	Mother's uterus	0	Not applicable
Estonia					
(Donchenko et al., 2005)	Alimentary	Unpasteurized goat or cow milk	Private breeding farm eaten in supermarket for promotion	44	Unvaccinated[β]
(Camprubi et al., 2020)	Alimentary	Unpasteurized goat or sheep milk	Goat and sheep farm	1	Unvaccinated
Finland					
(Wahlberg et al., 1989)	Handling of infected materials / blood infusion	Unclear/ blood transfusion	Laboratory / hospital	3 / 2	Not reported
Germany					
(Bodemann, 1977)	Handling of infected materials	During production of TBE antigen or transfer of infectious material to mice	Laboratory	2	Unvaccinated
(Brockmann et al., 2018)	Alimentary	Unpasteurized cow, goat, or sheep milk	Goat farm	2	Unvaccinated
(Chitimia-Dobler et al., 2021)	Alimentary	Unpasteurized goat milk	School goat farm	13	Vaccinated (n=1), Unvaccinated (n=12)
(Rieger et al., 1998)	Alimentary	Unpasteurized goat milk	Farms	50[%]	Unvaccinated[χ]
Hungary					
(Balogh et al., 2010)	Alimentary	Unpasteurized sheep, cow, or goat milk	Goat farm	31	Unvaccinated
(Caini et al., 2012)	Alimentary	Unpasteurized cow milk	Farm that was unauthorized to sell products	11[@]	Unvaccinated
(Szeles, 2008)	Alimentary	Unpasteurized goat milk	Shop who purchases from goat milk product producer	26	Unvaccinated
(Zoldi et al., 2013)	Alimentary	Unpasteurized goat or cow milk	Family farms	110	Not reported
Italy					
(Nicolini et al., 2011)	Alimentary	Unpasteurized cow milk	Not reported	1	Not reported
Lithuania					
(Juceviciene et al., 2002)	Alimentary	Unpasteurized goat or cow milk or products	Not reported	33	Unvaccinated
Poland					
(Jezyna et al., 1976)	Alimentary	Unpasteurized cow milk	Farm	13	Not reported
(Król et al., 2019)	Alimentary	Unpasteurized goat milk	Not reported	4	Unvaccinated
(Lipowski et al., 2017)	Solid organ transplant	Solid organ transplant	Hospital	3	Not reported
(Matuszczyk et al., 1997)	Alimentary	Unpasteurized goat milk	Farm	63	Unvaccinated
Slovakia					
(Bušová et al., 2018)	Alimentary	Unpasteurized goat or sheep milk	Not reported	5[$]	Unvaccinated
(Dorko et al., 2014)	Alimentary	Unpasteurized goat milk or milk products	Not reported	27[£]	Not reported
(Dorko et al., 2018)	Alimentary	Unpasteurized goat or sheep milk, goat or sheep cheese, or milk products	Sheep farm or restaurant or shop	146	Unvaccinated[α]
(Gresiková and Sekeyová, 1976)	Alimentary	Unpasteurized sheep milk products	Not reported	18	Not reported

(*continued on next page*)

Table 1 (*continued*)

Author, year	Mode of transmission	Potential source of infection or vehicle of infection	Setting of infection	Number of people with confirmed TBE*	Vaccination status of people with confirmed TBE
(Kerlik et al., 2018)	Alimentary	Unpasteurized sheep milk cheese	Not reported	169	Unvaccinated
(Kohl et al., 1989)	Alimentary	Unpasteurized goat milk or cheese	Farm	5	Not reported
(Kohl et al., 1996)	Alimentary	Unpasteurized goat cheese	Not reported	7	Not reported
(Labuda et al., 2002)	Alimentary	Unpasteurized goat or sheep milk or products	Not reported	334	Not reported
(Zaludko et al., 1994)	Alimentary	Unpasteurized goat milk	Not reported	14	Not reported
(Zavadska et al., 2018)	Alimentary	Unpasteurized goat milk	Not reported	20	Not reported
Slovenia					
(Avšič-Županc et al., 1995)	Handling of infected materials	Aerosol from blood	Laboratory	1	Unvaccinated
(Hudopisk et al., 2013)	Alimentary	Unpasteurized goat milk	Goat and sheep farm	4	3 unvaccinated, 1 vaccinated

* Number of cases of confirmed TBE via non-vectorial transmission
[$] 5 cases were positive via IgG (8 borderline), 7 cases were positive via IgM (18 borderline)
[£] Cases relating to the year 2012 was not included in the review as it is a duplicate of data within Dorko 2018 (Dorko et al., 2018) (n=15)
[@] 11 cases of 7 confirmed and 4 suspected cases of TBE
[%] number of cases relates to the number used within the case control study analysis
[α] vaccination status only reported in 6 cases
[β] vaccination status only reported in 27 cases
[χ] vaccination status only reported in cross-sectional survey cases

Table 2
Summary of the vehicle of infection in studies reporting alimentary route of transmission of TBEv.

Potential vehicle of infection	Studies assessing vehicle of infection with TBEv	Number of people with confirmed TBE
Single animal milk and/or milk products		
Unpasteurized goat milk and/or milk products	(Aendekerk et al., 1996; Chitimia-Dobler et al., 2021; Dorko et al., 2014; Hudopisk et al., 2013; Ilic et al., 2020; Knežević et al., 2019; Kohl et al., 1989, 1996; Krbková et al., 2015; Król et al., 2019; Markovinovic et al., 2016; Matuszczyk et al., 1997; Pazdiora et al., 2008; Pazdiora et al., 2012; Pazdiora, 1994; Rieger et al., 1998; Sixl et al., 1989; Szeles, 2008; Zaludko et al., 1994; Zavadska et al., 2018)	309
Unpasteurized sheep milk and/or milk products	(Gresiková and Sekeyová, 1976; Kerlik et al., 2018)	187
Unpasteurized cow milk and/or milk products	(Caini et al., 2012; Jezyna et al., 1976; Nicolini et al., 2011)	25
Multiple animal milk and/or milk products		
Unpasteurized cow, goat milk and/or milk products	(Donchenko et al., 2005; Holzmann et al., 2009; Juceviciene et al., 2002; Zoldi et al., 2013)	204
Unpasteurized goat or sheep milk and/or milk products	(Bušová et al., 2018; Camprubi et al., 2020; Dorko et al., 2018; Labuda et al., 2002)	486
Unpasteurized cow, goat, or sheep milk and/or milk products	(Balogh et al., 2010; Brockmann et al., 2018; Kříž et al., 2009)	97

et al., 2012; Chitimia-Dobler et al., 2021; Donchenko et al., 2005; Dorko et al., 2018, 2014; Ilic et al., 2020; Jezyna et al., 1976; Juceviciene et al., 2002; Kerlik et al., 2018; Kohl et al., 1989, 1996; Krbková et al., 2015; Kříž et al., 2009; Labuda et al., 2002; Matuszczyk et al., 1997; Pazdiora et al., 2008; Pazdiora et al., 2012; Pazdiora P, 1994; Sixl et al., 1989; Szeles, 2008; Wahlberg et al., 1989; Zaludko et al., 1994; Zavadska et al., 2018; Zoldi et al., 2013), one study was scored a moderate quality (Jezyna et al., 1976) and the remaining 25 studies were given a low rating. Of the three studies assessed using the analytical cross-sectional tool, one study had a moderate rating of quality (Bušová et al., 2018) and the remaining two studies had a low rating of quality (Gresiková and Sekeyová, 1976; Rieger et al., 1998). Details of the critical appraisal evaluation are included in Supplement S7.

4. Discussion

This systematic review of 41 studies confirms alimentary, handling infected material, and blood-borne as routes of TBEv transmission in addition to the main pathway through ticks. We found no evidence of vertical transmission from two studies (Dive et al., 2020; Ilic et al., 2020) and no studies were identified assessing sexual or other non-vectorial routes of transmission. Several central, north and eastern countries in Europe are currently considered endemic for TBE (European Centre for Disease Prevention and Control (ECDC), 2018), which reflects the range of European countries included within this review, with the majority of studies being reported from Slovakia and Czechia. The main route of non-vectorial transmission investigated in the studies was via milk products, with very few studies having reported handling infected material, vertical transmission (materno-fetal), or blood transfusion. The majority of alimentary TBE cases reported in this systematic review were from highly endemic TBE areas (European Centre for Disease Prevention and Control, 2021a). Seasonality, environment, competent vector abundance, and the presence of reservoir hosts are key elements for the transmission of the virus. This review included 1308 cases of non-vectorial transmission of TBEv, which represents a small proportion of the total number of cases reported to national health authorities across the years of publication of the included studies (1976-2021). Overall, no pattern in the number of cases via non-vectorial transmission were seen over time in the included studies, except in one study (Dorko et al., 2018) which reported an increase in the number of alimentary transmission of TBEv from 2012 to 2016 in Slovakia due to the consumption of unpasteurized goat, sheep or cow milk products. It is currently unclear whether this pattern is seen in other countries in more recent years. Most of the TBE cases described in this review are characterized by a biphasic phase character and most of the people infected were hospitalised. This could potentially indicate that alimentary infection could lead to a more severe manifestation due to the passage to the gastrointestinal tract or due to potentially higher infectious dose levels in milk (Dobler et al., 2012); however, given the lack of comparative data for vectorial transmission included in this systematic

Table 3
Characteristics of TBE cases via alimentary route of transmission from unpasteurized milk and products.

Author, year	Data	Number of cases	Characteristics of cases	Setting, Country	Month, Year	Hospitalisation
(Aendekerk et al., 1996)	Case report	1	54-year-old male	Not reported, Czechia	Not reported	1 hospitalised
(Balogh et al., 2010)	Outbreak	31	Not reported	Goat farm, Hungary	August 2006	0 hospitalised
(Brockmann et al., 2018)	Outbreak investigation	2	2 males	Goat farm, Germany	May 2016	2 hospitalized
(Camprubi et al., 2020)	Case report	1	18-year-old male	Goat and sheep farm, Estonia	July 2019	1 hospitalized
(Chitimia-Dobler et al., 2021)	Outbreak investigation	13	Not reported	School goat farm, Germany	April 2017	1 hospitalized
(Holzmann et al., 2009)	Outbreak investigation	7	3 male, 4 female, aged 7 to 65 years	Not reported, Austria	July 2008	4 hospitalised
(Hudopisk et al., 2013)	Outbreak	4	3 male, 1 female, aged 28-59 years	Goat and sheep farm, Slovenia	April 2012	2 hospitalised
(Jezyna et al., 1976)	Outbreak investigation	13	8 male, 7 female, aged 10-72 years	Farm, Poland	June 1974	13 hospitalised
(Kohl et al., 1989)	Outbreak	3	Not reported	Farm, Slovakia	May to June 1984	2 hospitalised
(Kohl et al., 1996)	Outbreak	7	Not reported	Not reported, Slovakia	September 1993	7 hospitalised
(Knežević et al., 2019)	Outbreak	5	1 male, 4 females, aged 10 to 85 years	Small family farm, Croatia	June 2019	3 hospitalised
(Król et al., 2019)	Outbreak	4	4 males, aged 24 to 36 years	Not reported, Poland	June 2017	4 hospitalised
(Markovinovic et al., 2016)	Outbreak	5	4 males, 1 female, aged 16 to 50 years	Family farm, Croatia	April 2015	5 hospitalised
(Matuszczyk et al., 1997)	Outbreak investigation	48	Not reported	Farm, Poland	May 1995	15 hospitalised
(Nicolini et al., 2011)	Case report	1	7-year-old male	Not reported, Italy	Not reported	1 hospitalised
(Pazdiora, 1994)	Outbreak investigation	3	Not reported	Family home, Czechia	July 1992	3 hospitalised

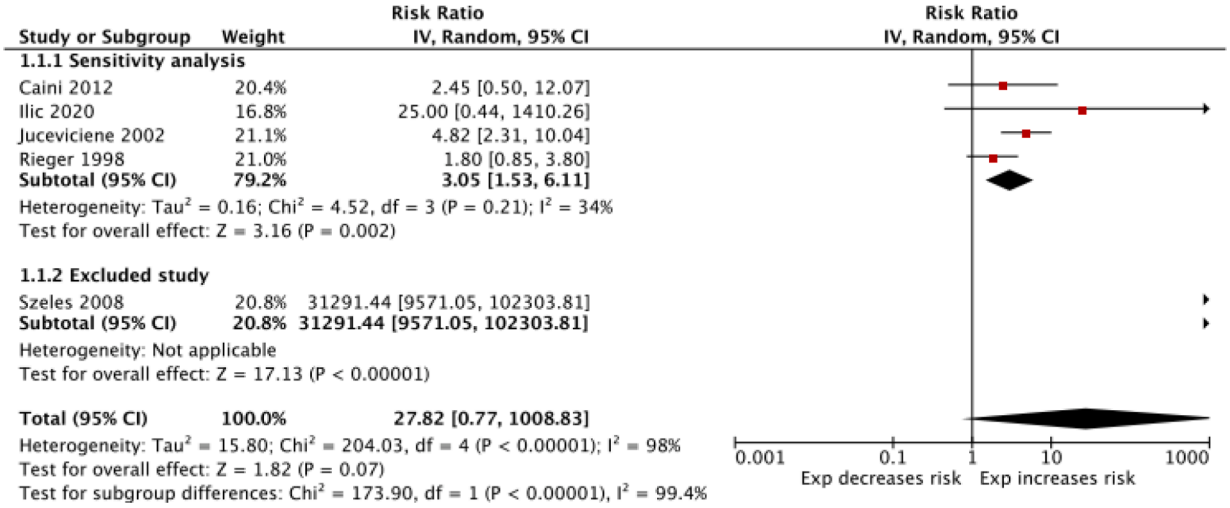

Fig. 2. Sensitivity analysis of the association between consumption of unpasteurized milk and products and the risk of TBE (excluding (Szeles, 2008)).

review, further investigation is needed to confirm or refute this hypothesis. Being vaccinated against TBE is the most effective measure to reduce the risk of contracting TBE if exposed to the virus (Heinz et al., 2013). Within the included studies, one vaccinated person was found infected, but his booster vaccination was overdue by 10 years, and therefore could be considered as unprotected at the time of the exposure (Chitimia-Dobler et al., 2021). Another study presents four people exposed to TBEv and the only exposed person who did not develop symptoms is the person who was vaccinated against TBE (Hudopisk et al., 2013). He had received his booster dose two years before exposure to the virus. The case was reported to have an absence of IgM, but high levels of IgG and a positive neutralising test, which could have been due to vaccine response. In general, regardless of the mode of transmission, the European Centre for Disease Prevention and Control (ECDC) reported that from 2015 to 2019, TBE notification rates were higher among males and among adults aged 45–64 years (European Centre for Disease Prevention and Control, 2021a). This could be related to the majority of infections transmitted by ticks and the more frequent outdoor activities or jobs of adult males compared to females (Jepsen et al., 2019; Slunge and Boman, 2018; Slunge et al., 2019). However, data on sex and age as reported in the studies included in this review, were not indicative of a predisposition of a person to be infected by a non-vectorial transmission route. A significant three-fold increase in the risk of TBEv infection was seen with the consumption of unpasteurized milk products; however, this meta-analysis only included four studies as part of a sensitivity analysis where the extreme outlier results from one study was excluded. Following World War II, numerous TBE outbreaks were reported due to ingestion of unpasteurised goat's milk given the rare availability of cow's milk (Dobler et al., 2012). More recently, TBE outbreaks have resulted from the consumption of unpasteurized milk products, believed to be healthier (Markovinovic et al., 2016) with several outbreaks resulting from the consumption of raw milk products

produced and distributed informally by family farms (Supplement S6). Other non-vectorial routes of TBEv transmission were also identified within this review. Three studies reported the transmission of the virus via the handling infected material in a laboratory setting (Avšič-Županc et al., 1995; Bodemann, 1977; Wahlberg et al., 1989). However, these cases date back to the 1970s to 1990s when the laboratory protective measures were unlikely to be as robust as current tools and methods. No transmission of TBEv in the laboratory setting were reported in the past two decades to the best of our knowledge. Additionally, we found only one study reported the transmission of TBEv to two people via blood transfusion from a person who was infected with TBEv in the period between 1959 and 1987 in Finland (Wahlberg et al., 1989). However, no data on the general screening procedures of TBEv in blood donors were found from our systematic review; therefore, further investigation of this could not be explored here. One study provides the first evidence of transmission of TBEv after solid organ transplant (Lipowski et al., 2017) suggesting the need of screening for TBEv before this type of procedure especially in endemic areas. Only two studies assessed vertical transmission (from mother to offspring) of TBEv (Dive et al., 2020; Ilic et al., 2020). In our review, there was no evidence of virus transmission from the infected mothers to the foetus or to the breastfed child. However, the authors of a general review of TBE (Dobler et al., 2012), reported that at least one case of transmission of TBEv was seen from an unvaccinated mother to her infant after birth via breast-feeding in Lithuania (Kunz, personal communication, 2002) but we were unable to confirm the validity of this case as this was reported anecdotally as a personal communication. In addition, in the former German Democratic Republic (Helpert and Sinnecker, 1966) a study reported three cases of TBEv infection in pregnant women with premature birth and foetal or neonatal intracranial haemorrhage with no investigation on infants' infection. One more case in Slovakia reported infection in a pregnant mother but the neonate was healthy, and he had not been infected (Hockickova et al., 2019). Research in rodents and goats has confirmed that TBEv can be excreted during the viraemic phase in milk (Dobler et al., 2012; Balogh et al., 2012); however, no similar data in humans was found in this systematic review.

4.1. Strengths and limitations of the systematic review

This systematic review has several notable strengths, including being conducted and reported according to JBI methodology (Aromataris and Munn, 2020) and PRISMA guidelines (Moher et al., 2009; Page et al., 2021), respectively. This will have minimized the risk of eligible studies being missed or excluded from the review, thereby maximizing the validity of the conclusions of the systematic review. However, there are some limitations. Although an exhaustive systematic search was conducted, for each country our findings are based on 10 or less studies. Additionally, even though our searches and screening processes did not impose any language restrictions, and translations were sought where necessary, we only identified eligible studies from 13 out of 30 countries, although it is acknowledged that not all of these countries have endemic TBE transmission. Also, there is the potential for under-reporting of cases due to differences in which cases were reported in different countries. For example, in 2012, Slovakia reported all cases including asymptomatic infection, whilst in Austria only cases with central nervous system involvement were reported (European Centre for Disease Prevention and Control, 2012). The methodological quality of the included studies varied, with only six studies being deemed as high quality; however, case report designs were generally found to score higher than other designs.

4.2. Prevention and mitigation measures

Future studies could use a standard, consistent case definition for TBE, such as the EU case definition (European Centre for Disease Prevention and Control (ECDC), 2018) to facilitate comparison between studies. At present, information on the route of transmission of TBEv is not requested to EU countries when they report TBE cases to ECDC. Therefore, to aid investigation into non-vectorial transmission of TBEv, it would be advantageous for local, regional and national authorities to collect robust data on the route of non-vectorial transmission (alimentary, handling infected material, transfusion, transplant, sexual, materno-fetal, breast feeding) and the vehicle of exposure for alimentary transmission (for example, unpasteurized cheese). However, as found in this review, the public health impact of non-vectorial TBE seems to be negligible compared to tick-borne transmission. Thus, it may be argued that scarce resources should be focused on preventing tick transmission. Studies on seroprevalence in domestic animals (e.g., goats, sheep, and cows) could also help confirm the circulation of the virus in these animal groups and could potentially help to better identify risk areas in addition to data on human cases and vector distribution obtained through routine surveillance efforts (Imhoff et al., 2015). Vaccination remains mainstay for the prevention of TBE and should be advocated in line with national health policies. The review suggests a systematic approach to documenting non-vectorial transmission of TBE and will be useful in identifying hotspot areas currently missed in the absence of reporting on the pathways of transmission. The burden of TBE from non-vectorial transmission is small in comparison to TBE from ticks, but it could be reduced further and potentially eliminated through sustained coordinated efforts in high endemic areas of Europe. This is key in view of the wider societal, environmental and climate change impacts that are already contributing to the expansion of vector occurrence in newer areas as well as their abundance. Finally, most cases of non-vectorial transmission were via alimentary route exclusively through the consumption of animal milk and products. It must be noted that having a foodborne TBE outbreak does not mean that the area is at high risk, but that people consumed a contaminated product in that place. Therefore, it is important to conduct a trace-back to find the vehicle of the infection together with the original source and the place where the animals could have been infected. In a study published after the end date of our searches, a new endemic area for TBE was identified in 2020 in France where a foodborne outbreak investigation detected a total of 42 cases of TBEv (Beaufils et al., 2020), where the patients became infected from eating unpasteurized goat cheese. Although we only identified one outbreak of TBE from the consumption of unpasteurized milk products available as a promotion item at a supermarket (Donchenko et al., 2005), several cases of TBE were reported from consuming products from farm shops. Other outbreaks of TBEv were seen in farming families where they consumed unpasteurized milk products from their own farms. In general, customers should be informed when the milk or its product is not pasteurised, to be aware when it could be dangerous to health from being potentially contaminated with TBEv and other pathogens including *Mycobacterium, Brucella, Coxiella, Escherichia, Salmonella*, and *Streptococcus*. The potential risk of TBE from consuming such products should be better communicated through effective community campaigns for awareness and appropriate public health advice for early detection of TBE symptoms. In the future, the vaccination of milk producing animals in endemic areas could be considered as a further way to protect consumers from the risk of alimentary TBEv (Salat et al., 2018).

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ttbdis.2022.102028.

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