ACM/1323 (revised)

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

DISCUSSION PAPER

Tick-borne encephalitis virus – draft risk assessment in relation to food

Issue

Tick-borne encephalitis virus (TBEV) in humans can infect the central nervous system and cause meningitis and encephalitis. Following the first ever detection of TBEV in the UK in 2019, an opinion was requested from the FSA by the Department of Health and Social Care (DHSC) and the Chief Medical Officer (CMO) on the risk to the public of infection with TBEV via the consumption of unpasteurised dairy products or of rare or undercooked meat from potentially infected animals in these areas.

The Agency prepared a draft risk assessment (Attached as Annex A) which estimated that the overall risk from consuming rare or undercooked meat or drinking RDM produced in the two areas was very low to low with a medium level of uncertainty. We also observed that for context the current ACMSF position is that the overall microbiological risk from RDM is low, and that the overall risk of TBEV via all foodborne pathways in the two affected areas is likely to be significantly lower than the risk from tick bite.

The Committee is invited to review this draft assessment and indicate whether it is in agreement with the Agency's conclusion.

Background

During a 2018-2019 survey of culled deer in England and Scotland by Public Health England, tick-borne encephalitis virus (TBEV) was detected in two areas of the UK: Thetford Forest and Hampshire/Dorset border [1]. This was the first detection of locally-circulating TBEV in the UK.

In addition, a 3-month-old German infant whose family spent their holiday in southern England from 1 to 15 July was hospitalised on 17 July with fever and diagnosed with meningitis. TBEV was diagnosed based on serology and travel history suggested exposure in the UK [2].

Infection with TBEV can cause tick-borne encephalitis (TBE), a viral infection involving the central nervous system. More detail about TBEV and TBE is in the hazard characterisation section of Annex A.

TBEV is normally transmitted by the bite of an infected *Ixodes ricinus* tick, which is the most abundant and widely distributed tick species in the UK. Ixodes ricinus is also the vector of louping ill virus (LIV) which is endemic in parts of the UK and complicates surveillance for TBEV in animals and humans due to serological cross-reactivity. This tick is also the vector for Lyme borreliosis. The presence of infected

ticks often varies over distances of several hundred metres for ecological reasons, making surveillance via tick collection difficult.

TBEV can also be acquired through the consumption of unpasteurised dairy products from infected animals, and may also but rarely be transmitted through transplants, blood transfusion and breastfeeding.

The Committee is asked:

To comment on the attached draft risk assessment; and

To advise whether it is in agreement with the Agency's conclusion that the overall 2-dimensional consideration of risk from TBEV from consuming rare or undercooked meat or drinking RDM produced in the affected areas is as follows:

1. Frequency of occurrence: very low (very rare but cannot be excluded)
2. Severity of detriment: medium (incapacitating but not usually life-threatening) to high (causing life-threatening or substantial sequelae or illness of long duration
3. Uncertainty relating to occurrence: high (scarce or no data)
4. Uncertainty relating to severity of detriment: low (solid and complete data available; strong evidence is provided in multiple references; authors report similar conclusions)
5. Remark on confidence in underlying science: key areas of uncertainty are the current UK distribution, the prevalence in sheep and cattle, the presence of infectious virus in meat and milk of affected animals, the persistence of virus in less than thoroughly cooked meat and the effect of cheesemaking processes on the viability of virus in dairy.

Secretariat
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Complete implementation of the extended multi-dimensional representation of risk agreed previously by ACMSF includes 5 steps;

- Assign the assessment of the frequency of occurrence for an adverse event to one of six exclusive and exhaustive categories for frequency (Negligible, Very Low, Low, Medium, High, Very High)
- Assign the assessment of the severity of the detriment for an adverse event to one of four exclusive and exhaustive categories of severity (Negligible, Low, Medium, High)
- In a remark assign the statistical uncertainty associated with the assessment of the frequency of occurrence to one of three exclusive and exhaustive categories of uncertainty (Low, Medium, High) and identify the exposed population that underlies the frequency assessment.
- In a remark assign the statistical uncertainty associated with the assessment of the detriment to one of three exclusive and exhaustive categories of uncertainty (Low, Medium, High) and identify variabilities in the populations that underlie the assessment of severity of detriment (particularly the populations of exposed individuals and harmful agents).
- In a remark address the level of confidence, doubt and caution surrounding the science that underlies the assessment of risk.

Risk Question

1. In light of evidence suggesting the strong likelihood of the circulation of tick-borne encephalitis virus (TBEV) in at least two areas of the UK, specifically:

- The detection and sequencing of TBEV RNA from ticks collected in the Thetford Forest region (Norfolk/Suffolk) and Hampshire/Dorset border,
- the observation of a high rate of seropositivity (up to 50%) by ELISA and HAI in blood samples taken from deer culled in the same areas, and
- a "highly probable" case of tick-borne encephalitis (TBE) in a 3 month-old German infant bitten by a tick in the New Forest in July 2019 and subsequently hospitalised with meningitis and seizures, an opinion is requested from the FSA by the Department of Health and Social Care (DHSC) and the Chief Medical Officer (CMO) on the risk to the public of infection with TBEV via the consumption of unpasteurised dairy products or of rare or undercooked meat from potentially infected animals in the two identified areas.

Hazard Identification

2. Tick-borne encephalitis virus (TBEV) is a virus capable of infecting humans and causing severe disease in 20-30% of cases, depending on strain. It can infect a range of mammals including rodents, wild and farmed ruminants, and humans.
3. In 2018-2019 an HPRU-funded study involving PHE collected blood samples from deer during culls in several counties in the UK, which suggested a high incidence (up to 50%) of TBEV seropositivity in some regions. As there is cross-reactivity between LIV and TBEV antibodies, engorged ticks were collected from culled deer within a 15 km radius of seropositive results and tested in pools of five adults or ten nymphs using reverse-transcriptase PCR (RT-PCR). Sequencing was attempted from positive results.
4. The study detected TBEV RNA in *Ixodes ricinus* ticks in the Thetford Forest Norfolk/Suffolk area of the east of England [1]:

- Surveys of questing ticks in Thetford Forest during 2018 were conducted and collected ticks pooled. Interim findings based on testing conducted up to July 2019, found that two pools were positive. A full-length genome of TBEV was obtained from one tick and phylogenetic analysis showed a European subtype related to the Norwegian Mandal strain of TBEV.
- A total of 2,485 ticks from the Hampshire/Dorset border were tested and one pool (in June 2019) was found to be PCR positive, giving a crude prevalence of 0.04%. The virus in the positive pool was sequenced and was most closely linked to the TBEV-NL strain detected in ticks collected in the Netherlands in 2015 [3]. This is a different TBEV strain from that found in the Thetford Forest, suggesting that at least two strains are present in the UK.
- In addition, a "highly probable" case of tick-borne encephalitis (TBE) in a German child, who was bitten by a tick in the Hampshire/Dorset border in July 2019, has been reported.

[1] Corrections were made to background information and paragraphs 1, 3 and 4 after the meeting

5. Serological evidence alone is not sufficient to prove the presence of TBEV due to the endemic presence of the related Louping ill virus (LIV) in parts of the UK; LIV antibodies show some cross-reactivity with those of TBEV [4]. However, the presence of TBEV in both these regions has been confirmed by subsequent virus-specific analyses (PCR and sequencing). It would appear to remain a possibility that the virus is circulating in other areas of the UK beyond those currently identified, but this is beyond the scope of the current risk assessment request.
6. The milk of infected ruminants may contain infectious virus, meaning that the primary foodborne exposure to the hazard is typically via unpasteurised dairy products such as raw drinking milk and other dairy products made from unpasteurised milk such as cheese and ice cream.
7. This risk assessment considers the risk to consumers of unpasteurised dairy products such as raw drinking milk and other dairy products made from unpasteurised milk such as cheese and ice cream, and of meat, originating from infected livestock including goats, sheep, cows and deer.

Exposure Assessment

8. Although the primary route of TBEV infection is via tick bite, foodborne transmission via dairy products originating from infectious ruminants (cattle, sheep and goats [5]) is known to occur. Cases of disease resulting from milk-borne transmission were common in the Czech Republic in the 1950s, and milk-borne TBE outbreaks have been reported in a number of other central and eastern European countries including Slovakia, Estonia, Austria and Hungary. Cases in Eastern Europe are more commonly reported to be associated with the consumption of unpasteurised sheep and goat milk (e.g. [6]), but the relative consumption patterns of unpasteurised sheep, goat and cattle milk in these areas is not available, meaning the relative risk from each species cannot be reliably estimated (**uncertainty**).
9. The main source of foodborne exposure to TBEV in an affected area is likely to be via drinking unpasteurised milk (raw drinking milk, RDM), with a lower likelihood of exposure via cheese and other products made from RDM or via milk which is inadequately pasteurised, but both of these are likely to be substantially lower than the likelihood of exposure via tick bite. Infectious TBEV has been detected in the milk of experimentally infected goats for 3-25 days post-infection and in cows and sheep for up to 8 days post-infection [7]. The infectious dose of TBEV via the ingestion of dairy products is not known, and little information is available on the mean or variation in virus typically present in unpasteurised milk or in cheese or other products made using it (**uncertainty**).
10. Both regions of interest have a low density of dairies, with only two Food Business Operators (FBOs) in the Ipswich (IP) postcode area registered to produce RDM (one from cow and one sheep) and another two (both cow) dairies registered to produce RDM in the New Forest area. The volume of potentially affected product is likely to be low and most is likely to be consumed locally; RDM can legally be distributed via farmers' markets or

direct online sales although the proportion sold online is believed to be low (expert opinion, FSA Approvals team).

11. As a virus, TBEV will not proliferate in stored dairy products under any conditions. Studies using goat milk experimentally spiked with Langat virus, a closely related virus used as a model of TBEV, suggest that TBEV is likely to be stable for several days in refrigerated milk but is inactivated within 1-2 days in milk kept at room temperature [8]. The same study suggests that high-temperature, short-time (HTST) pasteurisation should be highly effective at inactivating TBEV but that some residual virus might survive the thermal steps typically used in the cheesemaking process (**uncertainty**) [8]. Less evidence is available on the effects of heat, pH and water availability during cheese production, but a recent investigation of a cluster of TBE cases in Germany also confirmed the presence of infectious TBEV in unpasteurised cheese samples, although at a very low level [9]. The likely effect on infectious virus of the fermentation process used to produce yoghurt, kefir and similar foodstuffs is not known (**uncertainty**). Overall, virus stability in milk and dairy products will depend on storage conditions and time to consumption and this could impact on the dose ingested.
12. A 2013 EFSA scientific opinion reported finding no evidence suggesting meat-borne transmission of TBEV [10]. However, no studies were located that directly investigated this potential route of transmission experimentally or attempted the isolation of infectious virus from retail meat products (**uncertainty**). There is some evidence of increased antibody prevalence in abattoir workers in LIV-endemic areas [11] and historical reports suggesting LIV transmission to slaughterhouse workers and butchers [11], suggesting that infections resulting from exposure to infectious virus via meat might be possible but are extremely rare. Beef and lamb are often consumed rare which could increase the risk that virus present is not inactivated. Similarly, the infectious dose of TBEV via the ingestion of infected meat is not known, and little information is available on the mean or variation in virus typically present in raw meat, the rate of inactivation of virus during meat storage, or the effectiveness of less than thorough cooking (**uncertainty**).
13. The prevalence and incidence of TBEV in farmed ruminants in the area is highly uncertain (**uncertainty**). In some regions of the UK study, the estimated seroprevalence in deer samples was around 50%. The relationship between the prevalence in deer populations and the likely incidence in farmed ruminants is not clear (**uncertainty**), but goats have been found to be effective sentinels for detecting TBEV circulation, suggesting that goats and sheep are likely to be exposed in areas where TBEV is circulating [12, 13]. A small study in Poland in 2010 [14] found viral RNA in approximately 20% of milk samples from sheep and goats, and 10% of cattle, but a larger serological study in Germany suggests that TBEV has a highly patchy distribution resulting in considerable variation in incidence and prevalence results between flocks, meaning these figures should be extrapolated to the UK with caution (**uncertainty**). Infection with TBEV in cattle, sheep and goats is often subclinical [10], meaning animal inspections are not an effective method of detecting infection (**uncertainty**).

14. **Assessment 1 (Frequency of occurrence): Very low (very rare but cannot be excluded)**

15. **Remark 1 (Uncertainty in occurrence): High. This RA considers the population at risk via consumption of infected meat and unpasteurised dairy or products containing them. This depends on the distribution of the virus and the prevalence in livestock including goats, sheep, cows and deer in those areas. Few studies have been designed to estimate the frequency of foodborne infection in endemic regions and there are scarce or no data on key parameters, such as the consumption rate of unpasteurised milk in affected areas, the viral titre in the milk of affected livestock or the dose that is infectious via ingestion. There are also uncertainties around exposure via meat and meat products.**

Hazard Characterisation

16. TBEV is a virus in the genus Flavivirus transmitted primarily by Ixodes ticks. There are three subtypes of TBEV (European, Far Eastern and Siberia). Based on whole genome sequencing, both strains of TBEV detected in England fall within the subtype of TBEV found in western and central Europe, which is transmitted by the tick Ixodes ricinus (which is endemic in regions of the UK) and is associated with a slightly lower frequency of severe disease in humans than the far-Eastern and Siberian subtypes.

17. Approximately two-thirds of human TBEV infections are subclinical [15]; it is not known whether this is different following foodborne exposure. In clinical cases, the incubation period for TBEV is typically close to 8 days (range 4–28 days), although the incubation period is thought to be shorter (2-4 days) following foodborne exposure. This is followed by influenza-like illness typically lasting around five (2–10) days. In approximately 20-30% of cases involving the subtype detected in the UK, this progresses after an asymptomatic interval lasting seven (1–33) days to a second phase which may include fever, severe headache and/or paralysis and convulsions which may result in death or permanent sequelae such as paralysis. Mortality rates are up to 2%, and 10% of patients suffer long-term neurological complications, frequently with cognitive dysfunction and substantial impairment in quality of life.

18. In children, the second phase is usually limited to meningitis, whereas adults over 40 years of age are at increased risk of developing encephalitis, with higher mortality and long-lasting consequences in those over the age of 60. There is no specific treatment for TBE; rather, treatment relies on supportive management. Meningitis and encephalitis require hospitalisation. Available evidence suggests that immunosuppression can significantly increase the risk of severe disease or death [14].

19. A recent study estimated that each TBE case in Slovenia resulted in a burden of 3.1 DALYs [17].

20. **Assessment 2 (Severity of detriment) – Medium-High. Mortality rates are up to 2%, and 10% of patients suffer long-term neurological complications, frequently with cognitive dysfunction and substantial impairment in quality of life.**

21. **Remark 2 (Uncertainty in detriment) – Low. The clinical progression of TBEV and specifically the subtype detected in the UK is well-studied. TBEV infection is associated with a higher risk of mortality and long-lasting consequences in those over the age of 60 or with a weakened immune system but FSA advice is already that these groups avoid unpasteurised dairy.**

Risk Characterisation

22. The overall current risk to consumers of infection with TBEV from consuming rare or undercooked meat or drinking RDM produced in the two areas (Thetford Forest and New Forest) when considered in a 2-dimensional manner is estimated to be:

- Frequency of occurrence: very low (very rare but cannot be excluded)
- Severity of detriment: medium (incapacitating but not usually life-threatening) to high (causing life-threatening or substantial sequelae or illness of long duration
- Uncertainty relating to occurrence: high (scarce or no data)
- Uncertainty relating to severity of detriment: low (solid and complete data available; strong evidence is provided in multiple references; authors report similar conclusions)
- Remark on confidence in underlying science: key areas of uncertainty are the current UK distribution, the prevalence in sheep and cattle, the presence of infectious virus in meat and milk of affected animals, the persistence of virus in less than thoroughly cooked meat and the effect of cheesemaking processes on the viability of virus in dairy.

23. Several areas of key uncertainty are given below.

- Prevalence of infection in farmed ruminants in the affected area;
- Volume of milk produced by farmed ruminants in the affected area;
- Uses of this milk, particularly the volume used in the production of unpasteurised products (e.g. cheese) and RDM sales;
- The titre of infectious virus in fresh unpasteurised milk from an infected animal;
- The orally infectious dose of TBEV in dairy products;
- The effects of cheese production processes on the quantity of infectious virus present;
- The distribution of unpasteurised dairy products originating in this area to other areas via direct online sales.
- The titre of infectious virus in meat from infected animals and the rate at which this is inactivated after slaughter.
- From the information provided, it appears that serological results from deer not confirmed by PCR or sequencing results from the sampled ticks were discounted. It would be useful to confirm this and also to clarify the reason for discounting the other seroprevalence results, given the expected low

prevalence of infection in ticks and thus the risk of a false negative from tick surveillance.

Interpretation of probability categories used in this risk assessment taken from the new ACMSF 2-dimensional risk assessment framework ACM/1334

Frequency category	Interpretation
Negligible	So rare that it does not merit to be considered
Very Low	Very rare but cannot be excluded
Low	Rare but does occur
Medium	Occurs regularly
High	Occurs very often
Very High	Events occur almost certainly

Severity category	Interpretation
Negligible	No effects, or so mild they do not merit to be considered
Low	Mild illness: not usually life-threatening, usually no sequelae, normally of short duration, symptoms are self-limiting (e.g. transient diarrhoea)
Medium	Moderate illness: incapacitating but not usually life-threatening, sequelae rare, moderate duration (e.g. diarrhoea requiring hospitalisation)
High	Severe illness: causing life-threatening or substantial sequelae or illness of long duration (e.g. chronic hepatitis)

Qualitative categories for expressing uncertainty in relation to qualitative risk estimates

Uncertainty category	Interpretation
Low	There are solid and complete data available; strong evidence is provided in multiple references; authors report similar conclusions
Medium	There are some but no complete data available; evidence is provided in small number of references; authors report conclusions that vary from one another
High	There are scarce or no data; evidence is not provided in references but rather in unpublished reports or based on observations, or personal communication; authors report conclusions that vary considerably between them

Risk pathways

Raw drinking milk (RDM): TBEV survives relatively well in refrigerated milk and RDM is normally required to be consumed within 3 days of the point of sale, by which time infectious virus present at the time of production is likely to remain infectious. However, the affected areas have a low density of RDM production premises, with only two premises in the Ipswich postcode area and two more in New Forest postcode areas. Therefore, the risk to consumers of RDM derived from ruminants in the affected areas is considered to be **very low-low** with **medium** uncertainty deriving largely from uncertainty about the infectious dose in dairy products, the infectious dose initially present in the milk of an infected animal and the proportion of animals infected.

Cheese made from unpasteurised milk: The thermal processes involved in cheesemaking are likely to reduce, but not necessarily eliminate, TBEV in pasteurised milk. The effects of other processing steps are unknown. Therefore, the risk from consuming cheese made from unpasteurised milk from the animals in the affected area is **negligible-very low** with **medium** uncertainty, deriving largely from the uncertainty in the effects of cheese production and storage conditions on infectious virus.

Pasteurised dairy products: HTST pasteurisation is highly effective at inactivating TBEV in milk if carried out correctly. The risk from consuming pasteurised milk is therefore **negligible** with **low** uncertainty, the uncertainty largely deriving from the lack of data on the infectious dose typically initially present in the milk of an infected animal and the proportion of animals infected.

Rare or undercooked meat: Although a 2013 EFSA scientific opinion found no evidence suggesting meat-borne transmission of TBEV [10], the absence of studies that investigated this potential route of transmission experimentally or attempted the isolation of infectious virus from retail products and some evidence of LIV exposure in abattoir workers and butchers in LIV-endemic areas [9] suggests that there may be some risk of TBEV infection from eating rare or partially-cooked meat from infected animals. This risk is therefore assumed to be **negligible-very low** with **high** uncertainty.

Other food types: This assessment does not consider the risk from cream or fermented dairy products such as kefir.

Annex B: high-risk groups

TBEV infection is associated with a higher risk of mortality and long-lasting consequences in those over the age of 60 or with a weakened immune system [16]. The risk to these groups from pasteurised milk and dairy products remains negligible but, given the increased consequences of infection, there is an increased risk to these groups from the consumption of other products listed above. Current advice from FSA is already that elderly or immunocompromised individuals and pregnant women avoid unpasteurised dairy [18].

References

[1] https://wwwnc.cdc.gov/eid/article/26/1/19-1085_article

[2] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.47.1900679

[3] https://doi.org/10.1016/j.ttbdis.2018.10.008

[4] https://www.ncbi.nlm.nih.gov/pubmed/24690234

[5] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.3940

[6] https://www.ncbi.nlm.nih.gov/pubmed/19526924

[7] http://dx.doi.org/10.1159%2F000324023

[8] https://dx.doi.org/10.3389%2Ffbioe.2016.00040

[9] https://doi.org/10.2807/1560-7917.ES.2018.23.15.17-00336

[10] https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3266

[11] https://doi.org/10.1016/0163-4453(91)92756-U

[12] https://dx.doi.org/10.1186%2Fs12917-017-1136-y

[13] https://doi.org/10.1016/j.ttbdis.2011.09.011

[14] http://www.aaem.pl/Prevalence-of-tick-borne-encephalitis-virus-TBEV-in-samples-of-raw-milk-taken-randomly-from-cows-goats-and-sheep-in-eastern-Poland-,71646,0,2.html

[15] https://ecdc.europa.eu/en/tick-borne-encephalitis/facts/factsheet

[16] https://doi.org/10.1093/infdis/jix040

[17]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684505/

[18] https://www.food.gov.uk/business-guidance/raw-drinking-milk-hygiene-guidance