Public Health England

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Human Animal Infections and Risk Surveillance (HAIRS) group

Qualitative assessment of the risk that tick-borne encephalitis (TBE) virus presents to the UK human population

Updated March 2021

Contents

About the Human Animal Infections and Risk Surveillance group

This document was prepared by Public Health England (PHE) on behalf of the joint Human Animal Infections and Risk Surveillance (HAIRS) group.

HAIRS is a multi-agency cross-government horizon scanning and risk assessment group, which acts as a forum to identify and discuss infections with potential for interspecies transfer (particularly zoonotic infections).

Members include representatives from PHE, Department for the Environment, Food and Rural Affairs (Defra), Department of Health and Social Care (DHSC), Animal and Plant Health Agency, Food Standards Agency, Public Health Wales, Welsh Government, Public Health Scotland, Scottish Government, Public Health Agency of Northern Ireland and the Department of Agriculture, Environment and Rural Affairs for Northern Ireland.

See information on the risk assessment processes used by the HAIRS group.

*Due to resource limitations caused by COVID-19 response activities, this assessment has not been reviewed or signed-off by the Public Health Agency of Northern Ireland

Version control

Date of this assessment: March 2021

Version: 4.0

Reason for the assessment or update: Update on research and epidemiological data, including 2 probable autochthonous human cases in England (2019 and 2020) and further expansion of known geographical range of infected ticks in England

Completed by: HAIRS Secretariat and members

Non-HAIRS members consulted: Maya Holding, PHE

Date of previous risk assessment: July 2019

Date of initial risk assessment: March 2006

Summary

Overview

Tick-borne encephalitis (TBE) is a viral disease involving infection of the central nervous system in humans, and (though rarely) in some animals. Until 2019, the causative agent, TBE virus (TBEV), was not considered to occur in the UK. Since then infected ticks have been found to be present in defined areas of Thetford Forest in the East of England and on the Hampshire/Dorset border. In July 2019, a European visitor became ill after being bitten by a tick in the New Forest area and was subsequently diagnosed as a probable case of TBE infection. In July 2020, a second probable case of TBE infection was diagnosed in a patient from Hampshire.

Assessment of the risk of infection in the UK

Probability: Very low for the general population, Low for high risk groups (such as those living, working or visiting affected areas, as determined by duration of time spent outside)

Impact: Low

Level of confidence in assessment of the risk

High, with some uncertainty regarding current geographic distribution of infected ticks

Action(s) and recommendations

Raise local awareness on tick avoidance measures for the public and clinicians in known affected areas.

Consider seroprevalence studies amongst possibly exposed occupational groups.

Consideration of regionally appropriate follow-up to investigate evidence of historic and ongoing human TBEV exposure against a background of geographically varying presence of louping ill. This work should include evidence from veterinary surveillance and research activities which have focussed principally on sheep and grouse.

Further evidence-gathering from deer seroprevalence and tick testing, including from migratory birds.

Research into tick and virus ecology and tick transmission cycles.

Step One: Assessment of the probability of infection in the UK human population

This section of the assessment examines the likelihood of an infectious threat causing infection in the UK human population. Where a new agent is identified there may be insufficient information to carry out a risk assessment and this should be clearly documented. Please read in conjunction with the Probability Algorithm following the boxes shaded green in Annex A. Where the evidence may be insufficient to give a definitive answer to a question the alternative is also considered with the most likely outcome shown in solid colour and the alternative outcome in hatched colour. The text alternative to the probability algorithm can also be found in Annex B.

Is this a recognised human disease?

Outcome: Yes

Quality of evidence: Good

Tick-borne encephalitis (TBE) is a viral infection involving the central nervous system (CNS). It is caused by tick-borne encephalitis virus (TBEV), an RNA virus belonging to the genus Flavivirus that was initially isolated in 1937 in Russia.

Five main subtypes have been identified with differing geographic distributions: European or Western (TBEV-Eur), Siberian (TBEV-Sib), Far Eastern (TBEV-FE) (formerly known as Russian Spring Summer encephalitis), Baikalian (TBEV-Bkl) and Himalyan (Him-TBEV) (1-3). TBEV-Eur is endemic in rural and forested areas of central, eastern and northern Europe; TBEV-FE is endemic in far-eastern Russia and in forested regions of China and Japan; TBEV-Sib is endemic in the Urals region, Siberia and far-eastern Russia, and also in some areas in north-eastern Europe; and the recently described TBEV-Bkl found in East Siberia and Him-TBEV has been found in the Qinghai-Tibet Plateau in China (4).

In 2018 (latest full year data available), 3,212 cases (3,092 confirmed) were reported in Europe, including 16 associated fatalities (5). The highest incidence rates were reported in Lithuania, Slovenia and the Czech Republic. Comparison of trends over a five-year period shows that notification rates fluctuated annually and only Slovenia and Germany have seen a steady increase. In endemic regions of Europe, incidence varies considerably (6, 7). Annual peaks in incidence are correlated with seasonal periods of increased tick activity with the majority (92%) of cases reported between May and October (5, 7). Although cases continue to be diagnosed during the warmer months, there is no evidence of a major shift in seasonal pattern. Overall, case numbers are increasing across the region (7), associated with a variety of factors including climate change, an extended active tick season and habitat range of tick vectors, reforestation and an increase in outdoor leisure pursuits (6, 8). Improvements in case detection and reporting

may also be partly responsible for the increase (6). New foci of infections are also emerging with, for example, the Netherlands reporting TBEV for the first time in ticks, deer and a small number of autochthonous human cases since 2016, approximately 1 to 2 cases each year (9-12).

TBEV is transmitted mainly by *Ixodes spp.* ticks from a wild vertebrate host to humans and domesticated animals. The principal vectors are *Ixodes ricinus* (sheep tick) for TBEV-Eur. Human cases have been associated with consumption of unpasteurised milk or milk products from infected animals (13-15). TBEV is rarely transmitted from human-to-human via transplant (16), blood transfusion or breastfeeding (17). Animal studies have shown the potential for vertical transmission from an infected mother to the foetus (18). Infection has also been acquired accidentally in laboratories (19).

The incubation period of tick transmitted TBE is on average 7 days (a maximum of 28 days) but is shorter following foodborne transmission (approximately 4 days). The majority (around two-thirds of cases) of human TBEV infections are asymptomatic. In clinical cases, TBE often presents as a biphasic disease. The initial viraemic phase lasts approximately 5 days (range 2 to 10 days), and is associated with non-specific symptoms such as fever, fatigue, headache, myalgia and nausea. Following an asymptomatic interval of around 7 days, there is a second clinical phase involving the central nervous system (CNS) with presentations such as meningitis, meningoencephalitis, myelitis, paralysis and radiculitis (4).

Clinical presentation and outcomes differ across the distinct subtypes of TBEV (4, 20). TBEV-Eur is associated with milder disease, with 20% to 30% of symptomatic individuals experiencing the second CNS phase, and a case fatality rate (CFR) of less than 2%. However, severe neurological sequelae are observed in up to 10% of patients. In children infected with TBEV-Eur, the second phase of illness is usually limited to meningitis, whereas adults older than 40 years are at increased risk of developing encephalitis, with higher mortality and long-lasting sequelae in those aged over 60 years. TBEV-FE subtype is associated with more severe but monophasic illness, has a CFR up to 35%, and higher rates of severe neurological sequelae. TBEV-Sib subtype is associated with a less severe disease (CFR <3%), and a tendency for chronic or extremely prolonged infections (4). Haemorrhagic forms of the disease have been reported in the Asian part of Russia, but are thought to be rare (20).

Ticks are the primary route of transmission. Several *Ixodes* species of tick are both reservoir and vector for TBEV, spreading the virus between wild vertebrate hosts and occasionally transmitting TBEV to humans and domesticated animals. The principal vectors are *Ixodes ricinus* (sheep tick) for TBEV-Eur and *I. persulcatus* (Taiga tick) for TBEV- FE and TBEV- Sib. All tick stages can be infected, acquiring the virus from viraemic hosts during co-feeding, trans-stadially, trans-ovarially or transexually (21). I. ricinus is widespread in the UK, whereas *I. persulcatus* is considered absent.

New foci of TBEV infections in ticks can appear intermittent, as suggested by a Danish study which reported the apparent absence of the virus from a previously known area (22). TBEV prevalence in ticks in endemic areas can often be less than 1%, so lack of detection in tick populations may be due to low prevalence (23). Other studies have detected the virus in ticks along with seropositive animals, without evidence of infection in humans (24). Virus prevalence in ticks does not correlate with increased risk for human infection (25).

Sustained TBEV transmission cycles are thought to require co-feeding of larvae and nymphs on small mammal hosts, due to their short viraemic period of just 2 to 3 days. This is considered the main reason why TBEV does not occur throughout the geographical range of its tick vectors. Foci are thought to be limited geographically, and the areas may be as small as 0.5km2 (23). Larger hosts are also important for feeding and maintaining tick populations and, although not competent for the virus, can move infected ticks to new locations (26). Generally, in the UK, peak larval activity occurs after peak nymphal activity, however there is some field evidence that larval and nymphal I. ricinus show coincident co-infestation on small rodents. In a woodland study in southern England, co-infestation rates of ticks on small mammals were lower than in TBEV endemic parts of Europe, but it does demonstrate that co-infestation is possible in the UK and therefore transmission could occur (27).

Recent evidence of TBEV transmission in the Netherlands highlights that climatic and other environmental factors may have an impact on changing viral distribution to parts of western Europe.

Is this disease endemic in the UK?

Outcome: Yes – in ticks in high risk areas; No – not ubiquitous

Quality of evidence: Poor

Travel-related TBE cases are occasionally diagnosed in the UK; 7 confirmed cases were reported between 2014 and 2018 (28).

Although no confirmed autochthonous human cases (based on EU case definition) have been reported in the UK to date, since 2019 2 probable autochthonous cases of TBEV infection have been reported in England. In July 2019 a probable case of TBEV diagnosed through serology alone was reported in a German infant that had travelled to the New Forest (Hampshire) and acquired a tick bite (29). In July 2020, a second probable TBE case was reported in a patient who lives in Hampshire and recently acquired a tick-bite locally.

Louping ill virus (LIV), a related virus that displays a high degree of genetic homology to TBEV, is present in areas of the UK and can complicate surveillance for TBEV in animals and humans due to serological cross-reactivity between the 2 viruses.

The TBEV vector *I. ricinus* is a common tick found throughout the British Isles in woodlands, grazed grasslands, moor- and heath-land and some urban parks (see latest PHE map here) (30). Across Europe, although both TBEV (31) and *I. ricinus* (see latest ECDC map) have a wide distribution, TBE incidence is variable and does not occur in all areas where the tick is found.

In 2018 research conducted in England and Scotland detected evidence of TBEV for the first time through investigating deer seroprevalence, and by testing ticks (32). During 2018, ~1,300 deer serum samples from England and Scotland were tested by TBEV IgG ELISA and LIV haemagglutination inhibition assay (HAI). Blood-fed ticks from deer in areas with seropositive deer were tested by RT-PCR using a LIV/TBEV RNA assay, and a secondary LIV specific assay. Five ticks from the Thetford Forest area were TBEV PCR positive and a full-length genome of TBEV was obtained by sequencing from 1 of these.

Phylogenetic analysis confirmed the sequence to belong to the TBEV-Eu subtype; it is most closely related to the Norwegian Mandal strain of TBEV isolated from ticks in 2009 sharing a 99% sequence identity. Subsequent surveys of questing ticks in Thetford Forest were conducted, and collected ticks pooled. A small number of tick pools were positive. (A map of locations for seropositive deer and positive ticks removed from deer can be found in Holding et al, 2020 (32)).

Subsequently the presence of TBEV was detected in a questing tick pool in southern England in September 2019 at a location on the Hampshire/Dorset border (33). This virus is most closely related to TBEV-NL (LC171402.1), a strain of TBEV detected in ticks in the Netherlands in 2017.

The findings of TBEV in questing ticks in 2 parts of the country are consistent with the areas of higher deer seropositivity. This suggests that there is evidence of enzootic transmission of TBEV in certain foci in England. Ongoing serosurveillance of deer in 2020 for LIV/TBEV has again found the highest seropositivity in Thetford Forest (Norfolk/Suffolk) and New Forest (Hampshire). Further tick sampling is ongoing.

Are there routes of introduction into the UK?

Outcome: Yes

Quality of evidence: Good

In 2019, TBEV was found for the first time in ticks (questing and on deer) in the East of England, and then in ticks (questing) in Hampshire/Dorset (32, 33). The 2 detected viruses are of different lineages, indicating that at least 2 independent incursions have occurred.
There is potential for migratory birds to introduce TBEV infected ticks into the UK from endemic areas, as *I. ricinus* ticks infected with TBEV have been detected on migratory birds in Europe

(34). The virus has not been detected from samples taken from migratory birds in the UK (35) but surveys are ongoing.

There is also a possibility of TBEV introduction through animal movement, including companion animals, inadvertently transporting infected ticks. Changes in the PETS travel scheme in 2012 which removed compulsory tick treatment of companion animals entering the UK from Europe increased this risk.

Are effective control measures in place to mitigate against these routes of introduction?

Outcome: No

Quality of evidence: Good

Prevention of the introduction of infected ticks through animal movement would be necessary to mitigate the risk of TBEV introduction. However, it is impossible to prevent introduction of ticks via migratory birds.

The revised PETS travel scheme does not require the compulsory treatment of pets for ticks prior to return or entry to the UK. In recent years, public and animal health has focussed on education and awareness raising of this increased risk of importation of ticks with both veterinary professionals (via publications in veterinary journals and publications) and the general public (PHE tick poster). However, given the continued submissions of ticks from imported pets to the PHE Tick Surveillance Scheme (36), it can be presumed that imported ticks on pets, including those that have potentially travelled from or through TBEV endemic countries, will continue to present a risk of introduction of TBEV to the UK.

Do environmental conditions in the UK support the natural reservoirs or vectors of disease?

Outcome: Yes

Quality of evidence: Good

I. ricinus, both a reservoir and the vector of TBEV, is present and abundant throughout the UK (30). Transmission of TBEV is highly reliant on co-feeding of nymphs and larvae, and a recent study has shown some evidence of co-infestation (27). Climate change models also suggested a northern spread of TBEV in Europe (37).

Will there be human exposure?

Outcome: Yes – high risk groups; No – general population

Quality of evidence: Good

To date, 2 probable cases of TBEV human infections have been reported in Hampshire, England. Since infected ticks have been found in defined areas in Thetford Forest and Hampshire/Dorset, there is the potential for ongoing human exposure.

With these new findings, at risk groups for potential human exposure to TBEV infected ticks may now include those visiting, living or working in areas where infected ticks are present in the UK, and certain occupational groups may be at increased risk. Risk areas elsewhere in Europe are usually geographically limited due to co-feeding transmission that occurs on a small scale, sometimes as small as 0.5km2 (23). Exposure to infected ticks in the UK will likely be limited to similarly small foci.

There are farmed livestock of varied species on many premises within and around Thetford Forest and New Forest areas (Defra unpublished data). The number of dairy holdings (bovine and caprine) close to these areas registered for raw milk production is low, possibly 4 (FSA unpublished data). There is a theoretical risk of TBE through the food chain. The Food Standards Agency (FSA) has assessed the risk of infection with TBEV to consumers in 3 areas, which are:

- from drinking unpasteurised milk from cattle affected by TBE to be very low to low
- from cheese made from unpasteurised milk to be negligible to very low
- from consuming meat from animals affected by TBE to be negligible to very low

See comprehensive information on tick avoidance is on the GOV.uk website.

This advice was produced primarily for Lyme disease, but is cross-applicable given it is also transmitted by *I. ricinus*. Individuals can avoid exposure by using barrier methods when handling infested animals or entering tick infested environments. Protective measures include avoiding tick habitats, wearing long sleeves and trousers, using tick repellent or impregnated clothing, and checking frequently for ticks (38, 39).

Are humans highly susceptible?

Outcome: No

Quality of evidence: Good

Humans are susceptible to TBEV but the majority (two-thirds) of infections result in asymptomatic infection. TBEV-Eur is associated with milder disease than the other subtypes, with 20% to 30% of patients experiencing the second CNS phase and severe neurological sequelae is observed in up to 10% of patients. All age groups are susceptible but individuals of older age or with existing chronic conditions may be at higher risk of mortality and longer-term sequelae (38), and morbidity in children can be significant (20).

In TBEV endemic countries, a position paper by the World Health Organisation, suggests that TBEV vaccine should be offered to all age groups in highly endemic areas; those with incidence rates above 5 per 100,000 (40). Due to the potential for high morbidity in children, many countries recommend vaccination of children in TBEV endemic areas (6).

In the UK, a licenced TBE vaccine is available and is currently recommended only for those “at high risk of exposure to the virus”, through travel to endemic areas or employment (41-43). The Joint Committee on Vaccination and Immunisation is being asked to consider whether vaccination of high-risk groups such as forestry workers is warranted at this stage, while further studies looking for evidence of human exposure or infection are undertaken.

Outcome of probability assessment

The probability of human infection with TBEV in the UK population:

General population: very low

High risk groups (defined risk areas only): low

Step two: Assessment of the impact on human health

The scale of harm caused by the infectious threat in terms of morbidity and mortality: this depends on spread, severity, availability of interventions and context. Please read in conjunction with the Impact Algorithm following the boxes shaded green found in Annex C. Where the evidence may be insufficient to give a definitive answer to a question the alternative is also considered with the most likely outcome shown in solid colour and the alternative outcome in hatching. The text alternative to the impact algorithm can be found in Annex D.

Is there human-to-human spread of this pathogen?

Outcome: No

Quality of evidence: Good

TBEV is not directly transmitted from human-to-human, except in very rare cases via organ transplantation, blood transfusion or breastfeeding (16, 17). Human exposure to TBEV-Eur is primarily through the bite of an infected tick (*I. ricinus* in Europe) although foodborne transmission is occasionally reported (13-15). Accidental laboratory transmission has been reported (19).

Is there zoonotic or vector-borne spread of this pathogen?

Outcome: Yes

Quality of evidence: Good

I. ricinus is the primary vector for the TBEV-Eur transmission to humans, although foodborne transmission (mainly through contaminated unpasteurised milk) is occasionally reported (13-15).

For zoonoses or vector-borne diseases, is the animal host or vector present in the UK?

Outcome: Yes

Quality of evidence: Good

I. ricinus the tick vector for TBEV-Eur is present and abundant in the UK (30). Small mammals (for example rodents) that are able to support co-feeding transmission and large mammals (for

example sheep, goat, roe deer) which serve as important hosts for maintaining tick population are also present in UK.

Is the UK human population susceptible?

Outcome: Yes

Quality of evidence: Good

Humans are susceptible to TBEV (42), but approximately two-thirds of infections are asymptomatic.

Does it cause severe disease in humans?

Outcome: Yes

Quality of evidence: Good

Approximately two-thirds of human TBEV infections are subclinical, but the clinical spectrum ranges from mild disease (non-specific febrile illness) to CNS involvement (for example meningitis, severe meningoencephalitis with or without paralysis). Symptomatic infection can occur in all age groups, and is often more severe in adults, especially the elderly. The TBEV-Eur subtype is associated with milder disease compared to the other 2 virus subtypes.

TBE follows a typical biphasic course: a first viraemic phase with flu-like symptoms, followed by a period of quiescence, then the second phase with CNS involvement. Approximately a third of patients experience the second phase, and up to 20% of those with severe disease experience neurological sequelae. According to a 10-year follow-up survey, 80% of patients with primary myelitic disease will remain with sequelae (44). Overall the mortality rate is 0.5% to 2% (4).

Would a significant number of people be affected?

Outcome: No

Quality of evidence: Good

The vast majority of TBEV infections are acquired by tick bite, thus only those who are exposed to and bitten by infected ticks will be affected. To date, TBEV has only been found in defined areas of eastern and southern England, and exposure would be limited to those living in, working in or visiting those areas. While the vector *I. ricinus* is a common tick found throughout the British Isles, even in endemic countries, the rate of infection is relatively low (for example Germany 0.7/100,000; Austria 1.9/100,000; Lithuania 13.7/100,000) (28).

Are effective interventions (preventative or therapeutic) available?

Outcome: Yes

Quality of evidence: Good

Individuals can avoid tick bites by keeping skin covered as much as possible when visiting a tick-infested areas and using insect repellents. Consumption of unpasteurised dairy products should also be avoided in endemic areas. An effective and well-tolerated vaccination is available for protection against TBE and has been introduced into childhood immunisation schedules in endemic areas in Europe.

In the UK, a licenced TBE vaccine is available and is currently recommended only for those “at high risk of exposure to the virus”, through travel to endemic areas or employment (41-43). The Joint Committee on Vaccination and Immunisation is being asked to consider whether vaccination of high risk groups such as forestry workers is warranted at this stage, while further studies looking for evidence of human exposure or infection are undertaken.

There is no specific treatment for TBE. Supportive treatment can significantly reduce morbidity and mortality.

Outcome of impact assessment

The impact of TBE virus on human health in the UK: Low

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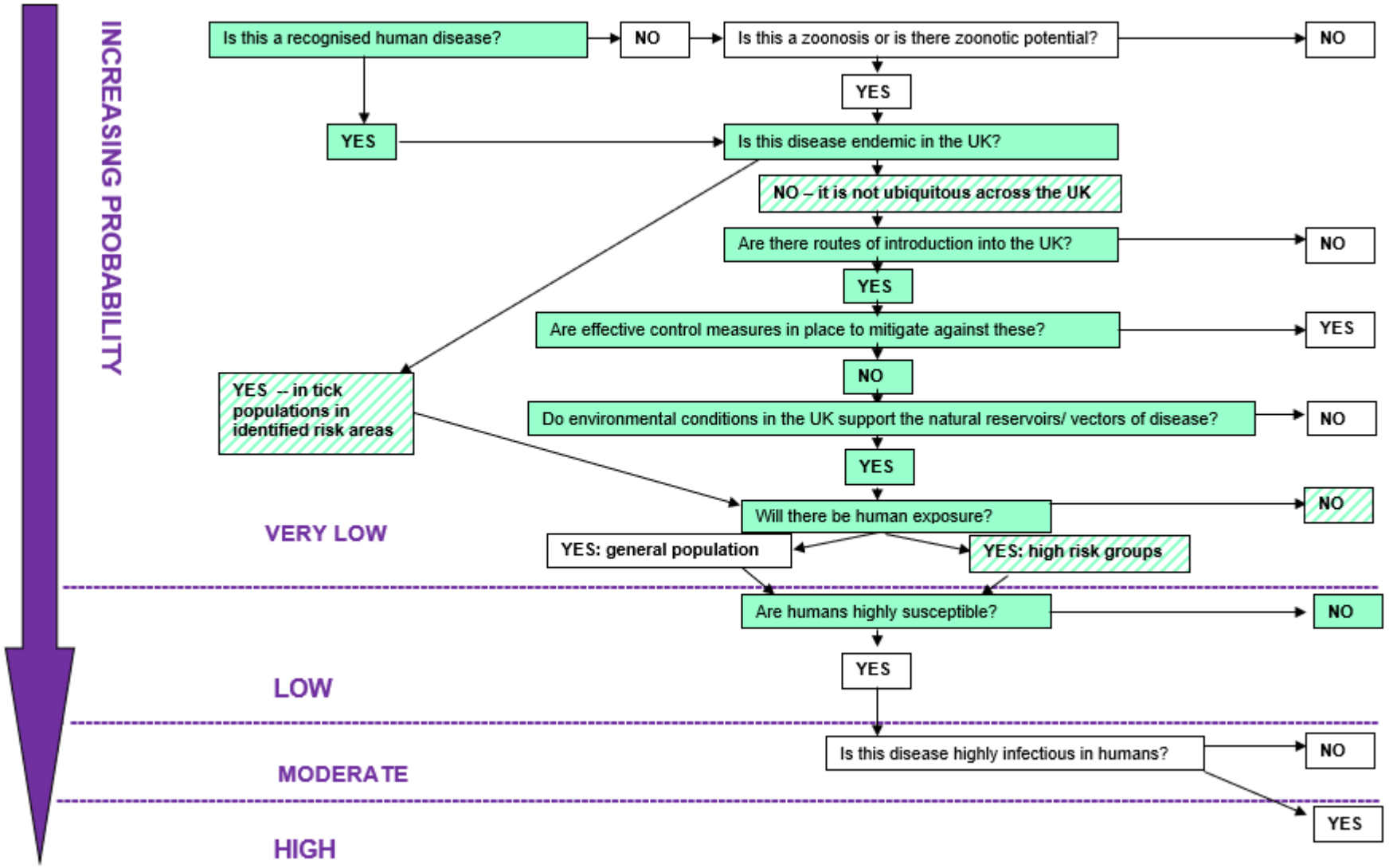
Annex A: Assessment of the probability of infection in the UK population algorithm



Accessible text version of the assessment of the probability of infection in the UK population algorithm

Outcomes are specified by a ✓ beside the appropriate answer. Where the evidence may be insufficient to give a definitive answer to a question, the alternative is also considered with the most likely outcome shown with ✓✓ and/or the alternative outcome(s) with a ✓

Question 1: Is this a recognised human disease?

Yes: go to question 3 ✓
No: go to question 4

Question 2: Is this a zoonosis or is there zoonotic potential

Yes: go to question 3
No: probability of infection in UK population is very low

Question 3: Is this disease endemic in the UK?

Yes: go to question 7 ✓
No: go to question 4 ✓

Question 4: Are there routes of introduction into the UK?

Yes: go to question 5 ✓
No: probability of infection in UK population is very low

Question 5: Are effective control measures in place to mitigate against these?

Yes: probability of infection in UK population is very low
No: go to question 6 ✓

Question 6: Do environmental conditions in the UK support the natural reservoirs/vectors of disease?

Yes: go to question 7 ✓
No: probability of infection in UK population is very low

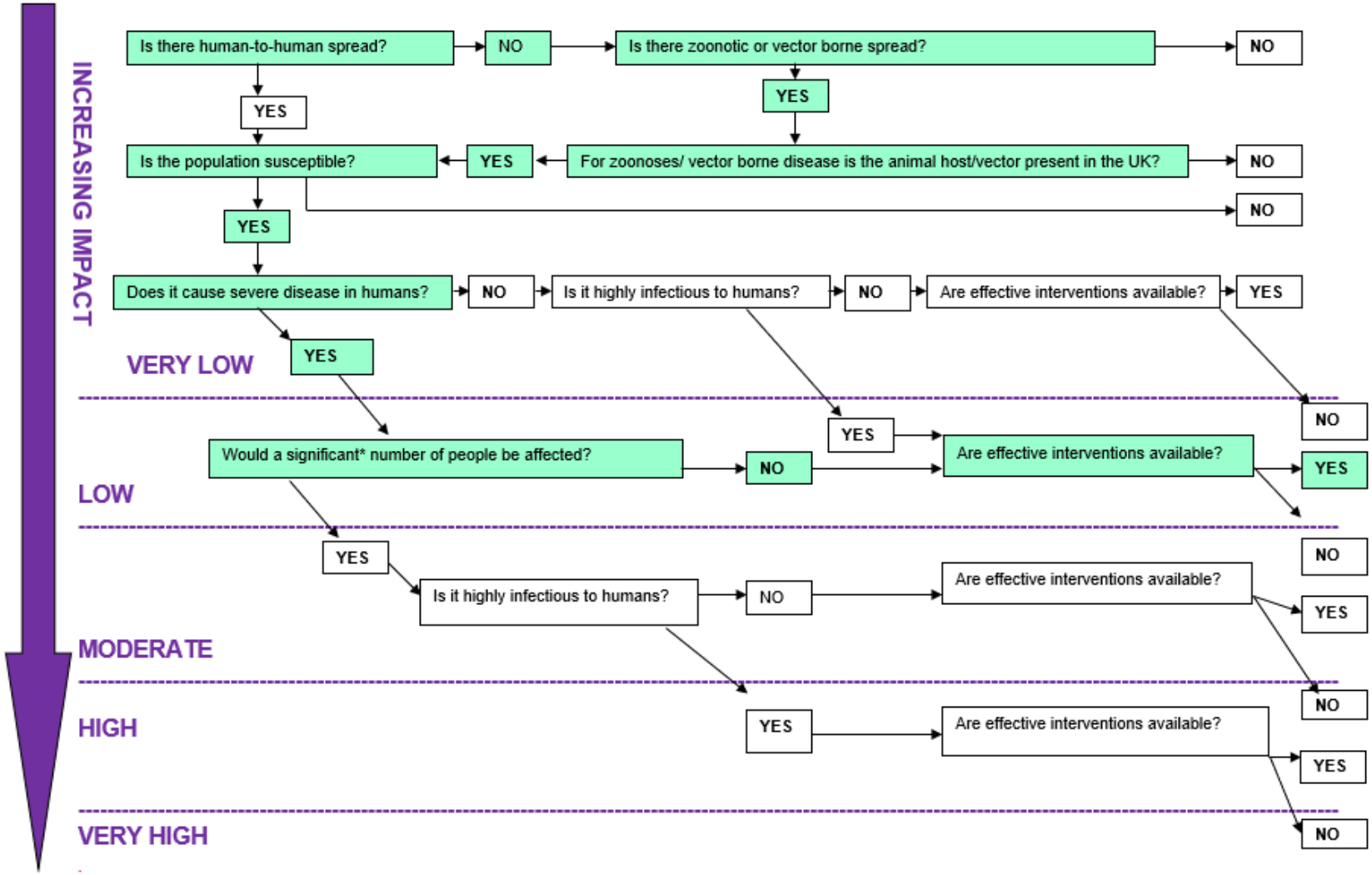
Question 7: Will there be human exposure

Yes: General population or high-risk groups: Go to question 8 ✓
No: probability of infection in UK population is very low✓

Question 8: Are humans highly susceptible?

Yes: go to question 9
No: probability of infection in UK population is low ✓

Annex B: Assessment of the impact on human health algorithm



*This question has been added to differentiate between those infections causing severe disease in a handful of people and those causing severe disease in larger numbers of people. 'Significant' is not quantified in the algorithm but has been left open for discussion and definition within the context of the risk being assessed.

Accessible text version of the assessment of the impact on human health algorithm

Outcomes are specified by a ✓ beside the appropriate answer. Where the evidence may be insufficient to give a definitive answer to a question, the alternative is also considered with the most likely outcome shown with ✓✓ and/or the alternative outcome(s) with a ✓

Question 1: Is there human-to-human spread?

Yes: go to question 4
No: go to question 2 ✓

Question 2: Is there zoonotic or vector borne spread?

Yes: go to question 3 ✓
No: impact on human health in the UK is very low

Question 3: Is the animal host or reservoir present in the UK?

Yes: go to question 4 ✓
No: impact on human health in the UK is very low

Question 4: Is the population susceptible?

Yes: go to question 5 ✓
No: impact on human health in the UK is very low

Question 5: Does it cause severe human disease?

Yes: go to question 8 ✓
No: go to question 6

Question 6: Is it highly infectious to humans?

Yes: go to question 9
No: go to question 7

Question 7: Are effective interventions available?

Yes: impact on human health in the UK is very low
No: impact on human health in the UK is low

Question 8: Would a significant number of people be affected?

Yes: go to question 10
No: go to question 9 ✓

Question 9: Are effective interventions available?

Yes: impact on human health in the UK is low ✓
No: impact on human health in the UK is moderate

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-leading science, research, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000

www.gov.uk/phe
Twitter: @PHE_uk
www.facebook.com/PublicHealthEngland

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Prepared by: HAIRS Secretariat, PHE on behalf of the HAIRS Group
For queries relating to this document, please contact: HAIRS@phe.gov.uk

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