Public Health England

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Human Animal Infections and Risk Surveillance (HAIRS) group

Qualitative assessment of the risk that *Mycobacterium lepromatosis* and *M. leprae* in red squirrels present to the UK human population

Version	1
Date	5 May 2017

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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.

This cross-government group is chaired by the PHE Emerging and Zoonotic Infections section. The HAIRS group 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 (DH), Animal and Plant Health Agency, Food Standards Agency, Public Health Wales, Welsh Government, Health Protection Scotland, Scottish Government, Public Health Agency of Northern Ireland and the Department of Agriculture, Environment and Rural Affairs for Northern Ireland.

About this risk assessment

Information on the HAIRS Group risk assessment processes can be found on the Public Health England website. https://www.gov.uk/government/collections/human-animal-infections-and-risk-surveillance-group-hairs

Date of this assessment	5 May 2017
Version	1.0
Reason for assessment	The recent detection of both *Mycobacterium lepromatosis* and *Mycobacterium leprae* in red squirrels in the UK.
Completed by	HAIRS scientific secretariat and members
Expert external contributors	Diana Lockwood, London School of Hygiene and Tropical Medicine Anna Meredith, Royal (Dick) School of Veterinary Studies, University of Edinburgh
Date of previous risk assessment	N/A
Date of initial risk assessment	5 May 2017

Summary of risk assessment for *Mycobacterium lepromatosis* and *M. leprae* detected in UK red squirrels

Overview	Both *Mycobacterium lepromatosis* and *M. leprae* have recently been detected in free-living red squirrels in the UK for the first time. Both pathogens are known to cause clinical illness in humans, however no human cases as a result of red squirrel contact have been reported in the UK to date.	
Assessment of the risk	**Probability**	High risk groups: Low General population: Very low
	Impact	Very low
Level of confidence in assessment of risk	High	
Action(s)/ Recommendation(s):	• Individuals identified as at higher risk of potential exposure to infected red squirrels in the UK should be advised of the risk and what measures can be taken to minimise the risk of transmission • Should any newly diagnosed leprosy cases be reported in the UK which are identified as potentially locally acquired, the patient(s) should be asked whether they had contact with red squirrels	

Assessing the risk to the UK population from new and emerging infections

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

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. 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.

QUESTION	OUTCOME*	QUALITY OF EVIDENCE
i) Are these recognised human diseases?	**Yes**	**Good**

Human disease: *Mycobacterium leprae* is a bacterium that causes the chronic infectious disease leprosy in humans (1). First identified in 1873, *M. leprae* is transmitted mostly through droplets during close and frequent contact; however it is not regarded as very infectious (2, 3). The incubation period is protracted but variable, normally around 5 years but can range to as many as 20 years (2). Symptoms of *M. leprae* are dependent on the immune response in the infected person and range from skin lesions, nodules, thickened dermis or skin infiltration, involvement of the peripheral nerves, to diffuse lepromatous leprosy (DLL). Untreated leprosy can cause permanent nerve damage (1, 2).

Diagnosis of leprosy is based on clinical suspicion, physical examination, histopathology and the use of PCR-based species specific assays as *M. leprae* is unculturable except by propagation in animals (4-6). Little information is available on mortality associated with leprosy as the disease is rarely a direct cause of death (7).

Cases of leprosy have historically been reported from every continent, except Antarctica. Out of 106 countries reporting cases of leprosy in 2015, 14 countries represented 95% of the global leprosy burden: Bangladesh; Brazil; Democratic Republic of Congo; Ethiopia; India; Indonesia; Madagascar; Myanmar; Nepal; Nigeria; Philippines; Sri Lanka; Mozambique and Tanzania (8). While the global prevalence of leprosy is reported to be decreasing, India recently reported an increase in the number of diagnosed cases (8). Within the UK, the last indigenously acquired case was reported in 1954 (9) but 192 imported cases of *M. leprae* infection from endemic countries were reported between 2000 and 2015 (PHE unpublished data).

In 2008, *M. lepromatosis* was identified as another causative agent of leprosy in humans, particularly DLL (10). *M. lepromatosis* is

most closely related to *M. leprae* (90.9% homology in the nucleotide region) and it is estimated that the two diverged around 10 million years ago (11). First identified in human cases in Mexico (10), it has subsequently been identified in Singapore, Canada, Brazil and Myanmar (12-16). Co-infections with *M. leprae* have been reported (14). Some studies report a higher morbidity and mortality associated with infection by *M. lepromatosis* and the resulting DLL, although the pathogenesis of this remains unclear (17).

Animal disease: Although humans are considered the main reservoir of *M. leprae*, naturally occurring infection has been reported in nine-banded armadillos, red squirrels (see (ii) below) and a limited number of non-human primates Infection with *M. lepromatosis* has also been reported in red squirrels in the UK and Ireland (see below) (18, 19). Before the detection of *M. leprae* and *M. lepromatosis* in red squirrels, neither mycobacterium species had been reported in animals in the UK. However, animal infections with two other mycobacteria (*M. lepraemurium* and *M. avium*) that can cause leprosy-like lesions in animals, particularly cats, have been reported in the UK, with *M. avium* the third most commonly cultured mycobacterium in cats behind *M. microti* and *M. bovis* (20).

In red squirrels, *M. lepromatosis* and *M. leprae* have been detected in overtly diseased as well as seemingly healthy animals. Both infections produce similar clinical signs (alopecia, extensive swelling of the snout, lips, eyelids, ear pinnae and limb extremities) and are therefore indistinguishable during ante and post mortem inspection, a feature also described in human cases. Both pathogens have been detected in tissue samples taken from different anatomical sites in clinically well squirrels and in those with leprosy features. With the exception of red squirrels, *M. lepromatosis* or *M. leprae* have not been detected in other animal species in the UK.

ii) Are these diseases endemic in the UK?	**Yes – animals only**	**Good**

Human population: Neither *M. lepromatosis* or *M. leprae* are endemic in the human population in the UK. Indigenous human cases of *M. lepromatosis* have never been identified in the UK. There have been no confirmed indigenously acquired cases of *M. leprae* reported in England and Wales since 1954. Prior to that, the last indigenously acquired case was reported in 1925.

Animal population: *M. lepromatosis* was first reported in red squirrels in Scotland in 2014 (19) and in England in 2015 on the Isle of Wight (21). In 2016, results of a study looking for the presence of *Mycobacterium* species in squirrels in Scotland, England and Ireland in samples collected between 2004 and 2015 confirmed the much wider geographical distribution of *M. lepromatosis* and, for the first time, *M. leprae*, in red squirrel populations in the British Isles (18). A follow-up study of red squirrel populations in the Isle of Wight between 2013 and 2016 detected on additional *M. lepromatosis* infected squirrel (died as a result of a road traffic

accident in 2016) (22). *M. lepromatosis* or *M. leprae* have not been detected in grey squirrels or any other populations of red squirrels outside the British Isles to date.

Phylogenetic analysis of the *M. lepromatosis* strains from Avanzi *et al*. (2016) (18) indicates that this pathogen is likely to have been present in red squirrels in the UK since at least 1820, and possibly earlier. Phylogenetic analysis of the *M. leprae* strain found on Brownsea Island determined that the closest relatives to this strain were from medieval Europe, including one strain detected in the skeletal remains of a leprosy victim buried around 730 years ago in Winchester, approximately 70 miles from Brownsea Island. Taken together, these preliminary analyses would suggest that *M. leprae* and *M. lepromatosis* may have been present in red squirrels for many hundreds of years, persisting long after *M. leprae* was eradicated from human populations in the British Isles.

Due to the popularity of red squirrels in the UK they are a highly observed species. Possible lepromatoid lesions have been seen and photographed by the public since 2010, and Avanzi *et al*., (2016) (18) state that these lesions are being increasingly observed. The first *M. leprae* PCR positive animals were detected in samples collected on Brownsea Island in 2010 and the first *M. lepromatosis* PCR positive animals were detected in samples taken in Scotland in 2011. It is unknown whether these mycobacterial infections are contributing to the decline in red squirrel populations in the British Isles.

iii) Will there be human exposure?	**Yes/No**	**Satisfactory**

It is illegal to capture or possess a wild red squirrel without a license (Schedules 5 and 6 of the Wildlife and Countryside Act 1981). Within the UK, there are collections of captive bred red squirrels, held under licence, often for release as part of conservation projects.

As a generally timid, tree-dwelling species that lives at low densities in a small number of habitats in the UK, general public contact with wild red squirrels is normally minimal. While there is an increasing trend for garden feeding of red squirrels in known habitat areas, human exposure in these circumstances would be predominantly through contact with their faeces or saliva. Direct contact with moribund or dead red squirrels may occur but very infrequently.

Human exposure to red squirrels is primarily restricted to those involved with the conservation of the species, those involved in providing care for wildlife (wildlife rescue or wildlife vets) and those responsible for the care of collections. These groups will have frequent and repeated direct contact with the species.

Thus, while it is unlikely that the general public will have contact with potentially infected animals, higher risk groups such as those involved in the care or conservation of red squirrels may be exposed. This is in contrast to the grey squirrels which, due to

their high densities and propensity for urban dwelling, have greater contact with humans.

To date, infection with *M. lepromatosis* and *M. leprae* has only been reported in wild squirrels in the UK. Therefore, people involved in the breeding or care of captive bred red squirrels may be less likely to come in contact with infected animals.

Transmission of *M. leprae* and *M. lepromatosis*

In humans, *M. leprae* and *M. lepromatosis* infections are primarily acquired through close and frequent contact with infected individuals via respiratory secretions. In red squirrels, it is not yet known how *M. leprae or M. lepromatosis* spreads within animals in a nest, but detection of *M. lepromatosis* in the lung (as well as in many other tissues) (18) indicates a possible respiratory mode of transmission. Although results are not available on testing of lung samples from *M. leprae* affected squirrels (currently restricted to pinna, muzzle and liver samples), it seems sensible to assume it will also have a respiratory mode of transmission in squirrels as it does with other mammals.

Although no incidents of zoonotic transmission of *M. lepromatosis* have been reported, multiple epidemiological case studies have provided evidence that contact with nine-banded armadillos is a risk factor for leprosy caused by *M. leprae* in the US, Mexico and Brazil (23-27). Evidence to support the zoonotic transmission of *M. leprae* from armadillos to humans includes the detection of the same unique genotype in both species living in the same area (26). Transmission from infected armadillos to humans is hypothesised to occur via direct and indirect contact with infected animals.

As the *M. leprae* detected in red squirrels in Brownsea Island in Dorset is the same sequence type as those seen in armadillos and humans (18), zoonotic transmission from red squirrels to susceptible humans may be possible. Phylogenetic analysis carried out by Avanzi and colleagues (18) indicates that both *M. leprae* and *M. lepromatosis* have been present in red squirrels in the British Isles for hundreds of years, although, to date, no cases of human infection among individuals with significant squirrel contact have been reported. Even with consideration of the lengthy incubation period for *M. leprae* and *M. lepromatosis* in humans, if transmission from infected squirrels to humans was occurring readily, cases of leprosy associated with wildlife contact would have been reported in the UK. However, if there has recently been a change in the epidemiology of *M. leprae* and *M. lepromatosis* infections in UK red squirrels with a subsequent increase in the risk of exposure and potential transmission to humans in contact with infected animals, it may be too soon to see an effect.

vi) Are humans highly susceptible?	**No**	**Satisfactory**

Although over 200,000 new human cases of leprosy are reported globally each year (the majority in South East Asia) (8), more than 95% of the world's population has natural resistance to development of disease caused by *M. leprae* (5). The genetic factors

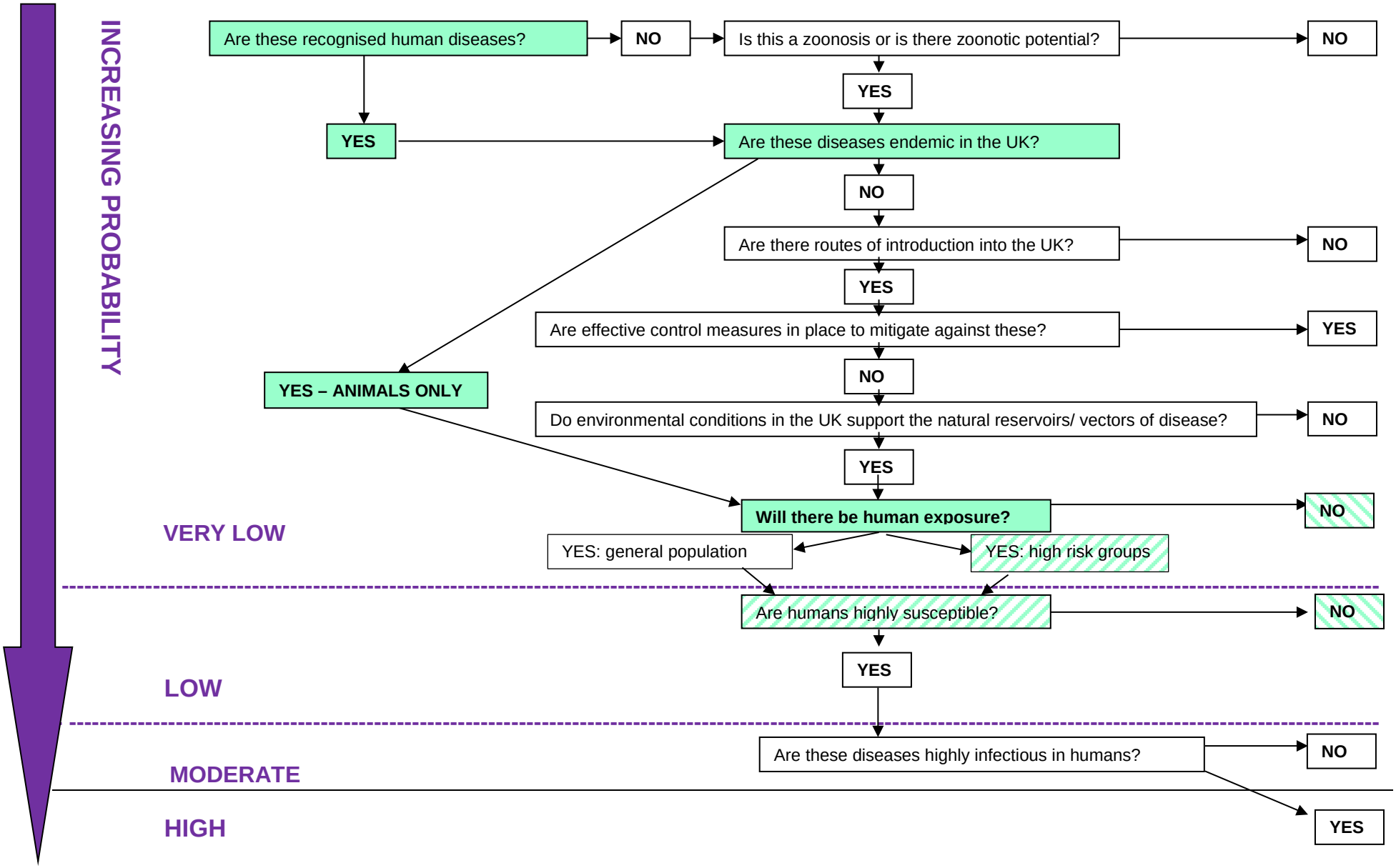
affecting immunity are not yet fully understood (28). As a relatively newly discovered pathogen, the rate of natural immunity in humans to *M. lepromatosis* has not yet been described.

The bacillus Calmette–Guérin (BCG) vaccine developed to protect against tuberculosis also provides protection against leprosy, although the magnitude and duration of protection is variable (29, 30). Introduced into the UK childhood vaccination schedule in 1953, vaccination of children aged 10-14 continued until 2005, when TB rates in the general population had fallen to such a low level that universal BCG vaccination was no longer needed. The current UK BCG vaccination programme is restricted to babies and children identified as at higher risk of exposure to M. tuberculosis (31).

Although zoonotic transmission of *M. leprae* has been described from nine-banded armadillos (although rarely reported), to date there has been no evidence to suggest similar transmission from infected red squirrels to in contact humans despite the hypothesised presence of this pathogen in wild red squirrel populations for many hundreds of years.

The **probability** of red squirrel-associated human infection with *Mycobacterium lepromatosis* and *M. leprae* in the UK population**: very low**

The **probability** of red squirrel-associated human infection with *Mycobacterium lepromatosis* and *M. leprae* in high risk groups**: low**


INCREASING PROBABILITY
Are these recognised human diseases?
NO
Is this a zoonosis or is there zoonotic potential?
NO
YES
YES
Are these diseases endemic in the UK?
NO
Are there routes of introduction into the UK?
NO
YES
Are effective control measures in place to mitigate against these?
YES
NO
YES – ANIMALS ONLY
Do environmental conditions in the UK support the natural reservoirs/ vectors of disease?
NO
YES
Will there be human exposure?
NO
YES: general population
YES: high risk groups
VERY LOW
Are humans highly susceptible?
NO
YES
LOW
Are these diseases highly infectious in humans?
NO
MODERATE
YES
HIGH

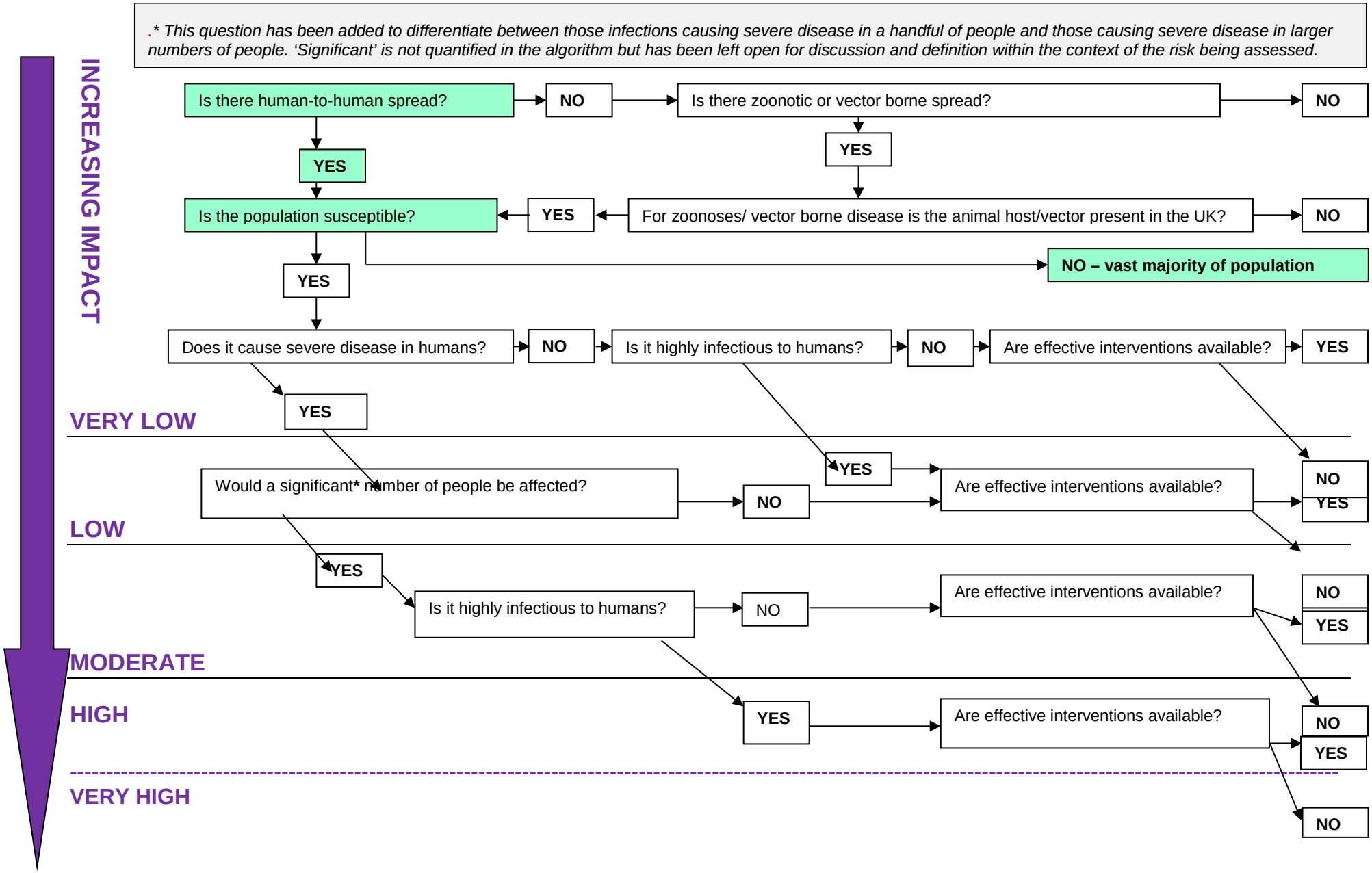
Step Two: Assessment of the impact on human health

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. 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.

Question	Outcome*	Quality of Evidence
i) Is there human-to-human spread?	**Yes**	**Good**
Human-to-human spread occurs via respiratory secretions following repeated, prolonged exposure to susceptible individuals. It does not spread through physical contact alone (32). Studies have shown that family members with a relative with leprosy, or people who share a house with them, are more likely to develop the disease (33, 34).		
ii) Is the population susceptible?	**No – vast majority**	**Satisfactory**
The vast majority of the UK population will not be susceptible to infection with *M. leprae* or *M. lepromatosis.* Up to 95% of people are reported to have immune-mediated resistance to leprosy (5). As a relatively newly discovered pathogen, the degree of natural immunity in humans to *M. lepromatosis* has not yet been described. The BCG vaccine has been shown to protect against *M. leprae* infection, but it's efficacy against *M. lepromatosis* is unknown. In the UK, BCG was part of the childhood vaccination campaign until 2005. Since then, BCG has only been administered to babies and children identified as at high risk of exposure to *M. tuberculosis*.		

The **impact** of red squirrel-associated human infection with *Mycobacterium lepromatosis* and *M. leprae* in the UK population**: very low**

If human infections were to occur in the UK, are effective interventions available?	***Yes***	***Good***
Suspected cases of leprosy identified in the UK would be referred to specialist services to confirm diagnosis and, if confirmed would be given appropriate treatment. Leprosy can be treated effectively by multidrug therapy. The treatment regimens recommended by the World Health Organization of six or 24 months' multidrug treatment (rifampicin, dapsone, and clofazimine) produce good clinical responses and low rates of relapse (35).		


.* 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.
INCREASING IMPACT
Is there human-to-human spread?
NO
Is there zoonotic or vector borne spread?
NO
YES
YES
Is the population susceptible?
YES
For zoonoses/ vector borne disease is the animal host/vector present in the UK?
NO
YES
NO – vast majority of population
Does it cause severe disease in humans?
NO
Is it highly infectious to humans?
NO
Are effective interventions available?
YES
YES
VERY LOW
YES
Would a significant* number of people be affected?
NO
Are effective interventions available?
NO
YES
LOW
YES
Is it highly infectious to humans?
NO
Are effective interventions available?
NO
YES
MODERATE
HIGH
YES
Are effective interventions available?
NO
YES
VERY HIGH
NO

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