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Human Animal Infections and Risk Surveillance group

Qualitative assessment of the risk that
variegated squirrel bornavirus 1 presents
to the UK population

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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 and Social Care (DHSC)
- 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
- Department of Agriculture Environment and Rural Affairs for Northern Ireland

Risk assessment document management

Date of this assessment	June 2019
Version	2
Reason for update	Further details on the incidents in Germany published, with new cases identified
Completed by	HAIRS scientific secretariat and members
Date of previous risk assessment	24 August 2018
Date of initial risk assessment	September 2015 (zoonotic potential)

Information on the risk assessment processes used by the HAIRS group can be found at <https://www.gov.uk/government/publications/hairs-risk-assessment-process>

Summary of risk assessment for VSBV-1 and its impact on the UK population

Background	Since initial detection in 2015, variegated squirrel bornavirus (VSBV-1) has to date been detected in 5 squirrel species and associated with 4 confirmed, 1 probable and 2 possible human infections.	
Summary of the assessment	Probability	UK general public: Very low High risk group: Low
	Impact	Low to moderate
Level of confidence in assessment of risk	Satisfactory	
Action(s)/ Recommendation(s):	<p>Communicate the outputs of this risk assessment to the British and Irish Association of Zoos and Aquariums (BIAZA), UK Zoo Federation, British Veterinary Zoological Society (BVZS), and the International Zoo Veterinary Group (IZVG), so that risk can be communicated to members with implicated squirrel species in their collections.</p> <p>In the absence of a known organisation covering small exotic animal collections, key veterinary pathologists who deal with exotic animals should be informed.</p> <p>Continue to monitor scientific literature for detection of VSBV-1 in other squirrel species.</p> <p>Continue to monitor scientific literature for human illness associated with VSBV-1.</p>	

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

Step 1: Assessment of the probability of infection in UK population

The likelihood of an infectious threat causing infection in the indigenous 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. 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 this a recognised human disease?	Yes	Good
<p>The <i>Bornavirus</i> genus includes 8 host class specific virus species, 2 of which contain 3 viruses known to affect mammals – Borna disease virus 1 and 2 (BoDV-1 and BoDV-2), belonging to <i>Mammalian 1 bornavirus</i> and variegated squirrel bornavirus 1 (VSBV-1) belonging to <i>Mammalian 2 bornavirus</i> ^[1].</p> <p>VSBV-1 was first reported in 2015 following reports of the first 3 human cases to die of encephalitis of unknown aetiology but with similar clinical symptoms in Germany between 2011 and 2013 ^[2]. The novel virus (VSBV-1) was first detected via metagenomic analysis of brain and other tissues from a variegated squirrel (healthy, accidental death) owned by 1 of the 3 fatal cases of acute encephalitis.</p> <p>The natural host and the geographical range of VSBV-1 have not yet been identified. To date, VSBV-1 has been detected in 5 squirrel species, endemic to South East Asia and Central America, in private and zoological collections in Europe: the variegated squirrel (<i>Sciurus variegatoides</i>), Prevost’s squirrel (<i>Callosciurus prevostii</i>), Finlayson’s squirrel (<i>Callosciurus finlaysonii</i>), Swinhoe’s striped squirrel (<i>Tamiops swinhoei</i>) and the Red-tailed squirrel (<i>Sciurus granatensis</i>) ^[3, 4]. Infected squirrels have been identified in captive collections in Germany, the Netherlands, and Croatia. Squirrels positive for VSBV-1 do not show any signs of clinical infection, therefore any positive detections would be as an incidental finding or as a result of</p>		

specific screening for VSBV-1. Of note, some of the tested squirrels in Germany became RNA-positive on repeat sampling several months after first testing negative ^[3].

Four human cases of confirmed VSBV-1 infection have been reported to date ^[2, 5]. All had slow onset, progressive and ultimately fatal encephalitis. All were reported from Germany, in individuals with regular contact with variegated or Prevost's squirrels. The initial 3 cases (occurring between 2011 and 2013) were men (aged 63, 62 and 72 years old) who resided in the state of Saxony-Anhalt, central Germany and all were breeders of variegated squirrels ^[2]. Molecular and immunohistochemical analysis of brain samples from the 3 deceased patients confirmed the presence of gene sequences identical to sequences found in the genome of the squirrel. The patients were known to each other, met regularly, belonged to the same private squirrel breeding association, traded squirrels and had similar exposures to variegated squirrels.

In June 2018, the fourth fatal human case of VSBV-1 infection was reported in Schleswig-Holstein, northern Germany ^[5]. This individual was a 45-year-old female German zoo animal handler, who had died in 2013 of a myeloencephalitis of undetermined aetiology. The infection was identified following retrospective investigations triggered by the detection of VSBV-1 in a Prevost's squirrel belonging to the zoo's collection, with which the case had frequent contact. VSBV-1 detected in stored tissue samples from the patient were found to cluster with sequences taken from the zoo's infected Prevost's squirrel with approximately 99.9% sequence identity. This was the first reported case of occupational VSBV-1 infection and the first human infection associated with Prevost's squirrel contact.

In February 2019, 1 probable and 2 possible cases of human VSBV-1 infection were reported. ^[6] These had been detected during trace-back animal trade investigations, case-finding and serological testing of individuals with exotic squirrel contacts in Germany. The 2 possible cases were both squirrel breeders who had died of encephalitis in 2005 and 2006, without any pathogen being identified at the time. Both were males over 60 years of age with co-morbidities, and each kept both variegated and Prevost's squirrels. No laboratory samples remained for testing, and thus they were classified retrospectively as possible VSBV-1 cases. The probable case, also a squirrel breeder, was identified when he tested positive on serological testing. He was a healthy man in his 40s, who had had an illness with fever and prolonged headache and neurological signs in 2004. He had anti-VSBV-1 IgG antibodies (IFAT, ELISA and immunoblot) and VSBV-1 specific memory T-cells. While the pathophysiology is unknown, immunopathology of fatal VSBV infections has recently been described. ^[7] Histological tissue analyses demonstrated panencephalitis in all 4 such cases, with widespread viral RNA and antigen deposition. Sequential CSF analyses showed pleocytosis, elevated protein and lactate, and intrathecal specific antibody production.

Cranial nerve RNA and antigen positivity was shown for the only patient who had this tissue examined, but it is not known if this resulted from spread from the brain, or from intranasal route of viral entry. The patient with the highest viral load and most severe inflammation had the shortest clinical course. Taken together, the authors concluded that their findings indicate a T-cell mediated immunopathology in fatal human VSBV-1 infection.

The mode of transmission of VSBV-1 from infected squirrels to human handlers has not been determined, but has been hypothesised as being via bites or scratches [2], or possibly via contaminated litter [3]. The highest viral loads in squirrel tissue have been detected in the central nervous system, but RNA was also detected in samples from excretory organs such as salivary glands, bladder and kidneys, as well as the skin, nose and sex organs [3, 4]. However, infective viral particles have yet to be demonstrated in animal secretions or skin samples.

ii) Is this disease endemic in the UK?	No/Unknown	Satisfactory
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Confirmed, probable and possible human cases of VSBV-1 infection have only been reported in Germany to date. [2, 5, 6]

Of the 5 VSBV-1 implicated squirrel species, only 2 are present within collections held by British and Irish Association of Zoos and Aquariums (BIAZA) members (Prevost’s squirrel and Swinhoe’s striped squirrel). It is possible that further collections of these or other squirrel species implicated in VSBV-1 may be present in the UK in collections not registered with BIAZA and for which data are therefore not available. Within Europe, there is a growing trend for keeping exotic squirrel species as pets. There is evidence to suggest that Prevost’s and Swinhoe’s striped squirrels, and possibly other exotic squirrel species, are kept in private collections in the UK as pets [8, 9].

We are not aware of any BIAZA registered UK collections of either Prevost’s squirrels or Swinhoe’s striped squirrels that have been tested for VSBV-1. Testing of a small number of red (*Sciurus vulgaris*) and grey squirrels (*Sciurus carolinensis*) from the UK failed to detect the presence of VSBV-1 [4]. The virus has never been detected in either red or grey squirrels tested from other European countries (261 red and 12 grey squirrels sampled to date) [3].

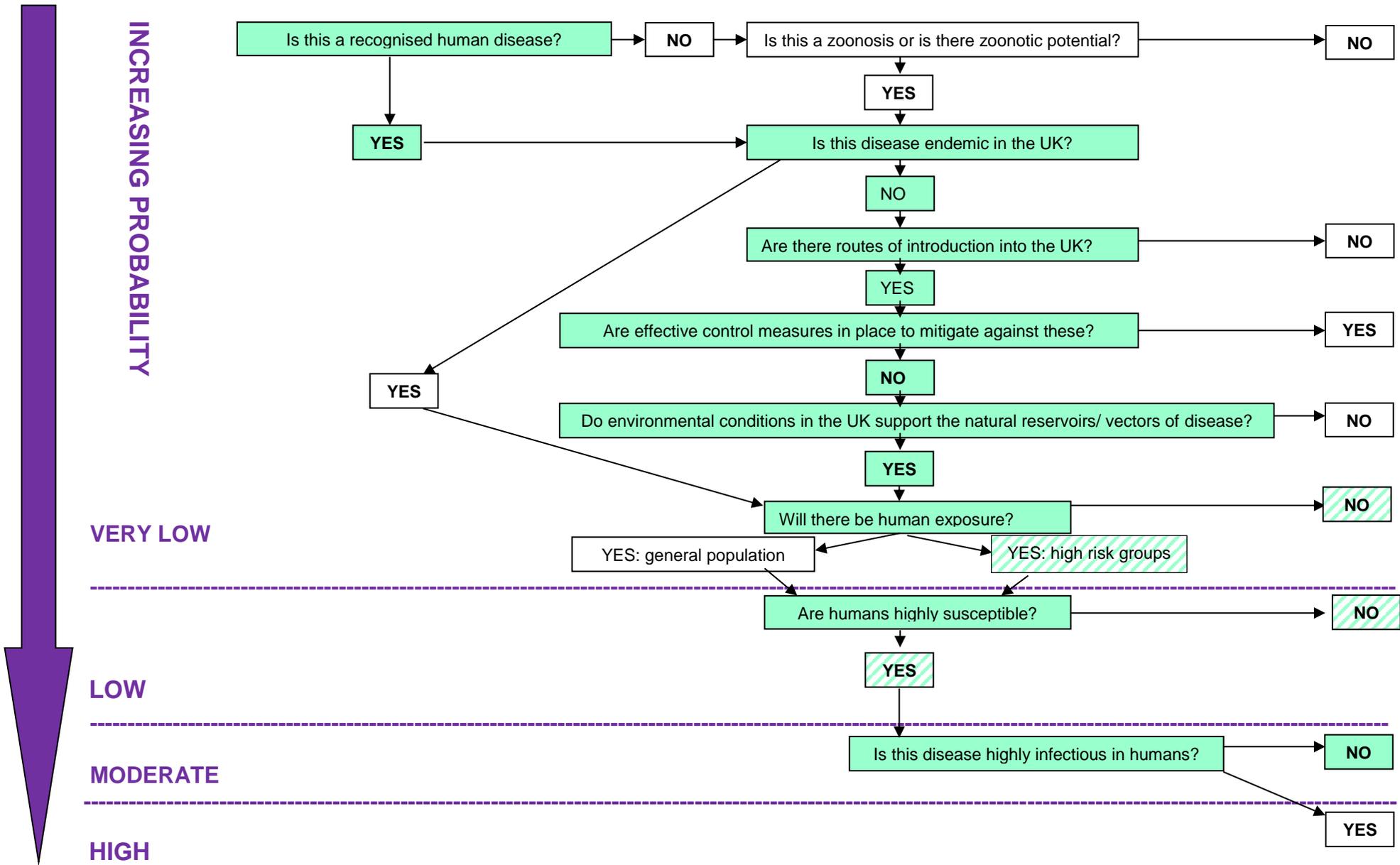
iii) Are there routes of introduction into the UK?	Yes/presumed	Satisfactory
<p>To date, VSBV-1 has been detected in 4 confirmed, 1 probable and 2 possible human cases (all in Germany) and in 5 distinct exotic squirrel species of South American and Asian origin, in Germany, the Netherlands and Croatia. Some of these squirrels are known to have been imported into identified collections in Germany from Costa Rica in 1999, and southeast Asia in the 1980s. ^[6]</p> <p>Since no incidents of human-to-human transmission have yet been reported, the main route of introduction into the UK with potential for onward transmission to humans would be via an infected squirrel/squirrels. Within the UK, small numbers of the implicated squirrel species are present in BIAZA members' collections however, it is recognised that further animals may be present in other private and public premises (unregistered with BIAZA).</p> <p>It has not been possible to determine how many and from where these exotic squirrel species have been imported into the UK as they are not covered by Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) import rules and would be imported as unspecified rodents. The risk of importing an infected animal may be reduced by pre-import screening for VSBV-1 although repeat sampling after 3 months is recommended due to the possibility of intermittent shedding and/or latent infection with stress activated excretion ^[3].</p> <p>The source of infection for the implicated squirrel species has yet to be identified. No specific nucleotide variations within the VSBV-1 genomes have been observed within the different squirrel species or subfamilies, indicating the possibility of a common source ^[3]. Hypotheses for the introduction of this virus into Europe include:</p> <ul style="list-style-type: none"> • VSBV-1 is ubiquitous in the implicated, and possibly other, exotic squirrel species and was introduced into European collections by an imported animal(s) • VSBV-1 could have been introduced into squirrel collections in Europe by another subfamily (as yet unidentified) with transmission facilitated within and between collections by poor biosecurity, shared facilities or via handlers/carers • an as yet unidentified European reservoir host 		

iv) Are there effective control measures in place to mitigate against these?	No	Satisfactory
<p>There are currently no restrictions on the importation of exotic squirrel species from European countries. Pre-import screening for VSBV-1 may be possible. Of note, some of the squirrels in Germany became RNA-positive on repeat testing several months after first testing negative [3]. The Friedrich Loeffler Institute in Germany has developed a PCR to detect VSBV-1 in mouth swabs and faecal samples from squirrels allowing for detection in live animals.[6]</p>		
v) Do environmental conditions in the UK support the natural reservoirs/vectors of disease?	Yes	Good
<p>The natural reservoir of VSBV-1 has not yet been determined. It is not known whether populations of the implicated species are naturally infected. Some of the exotic squirrel species implicated in VSBV-1 are present in UK zoological and private collections.</p>		
vi) Will there be human exposure?	High-risk groups only	Good
<p>Based on currently available information, human exposure will be restricted to those with significant contact with the infected squirrel species. There is therefore no risk to members of the public. No antibodies were detected amongst 150 German blood donors tested.[5] There is also currently no evidence of human-to-human transmission, but the risk from this route of transmission cannot be stated with certainty at this time.</p> <p>All 4 confirmed human cases of VSBV-1 were reported in individuals with close and frequent contact with variegated or Prevost's squirrels, and 3 had underlying co-morbidities. The additional probable and possible cases were also breeders with prolonged close contact with exotic squirrels. A small-scale serological study involving 14 animal handlers at the zoo where the occupational exposure case was employed failed to detect any further human cases or evidence of past exposure[5]. Seroprevalence studies of zoo workers and squirrel breeders and their households were undertaken in Germany.[6] A single seropositive individual was detected amongst 14 breeders, 9 household members and 24 zoo animal caretakers. This was the squirrel breeder who was subsequently classified as a probable VSBV-1 case.</p>		

vii) Are humans highly susceptible?	Probably not	Poor
<p>Humans can be infected, but there is currently insufficient information to accurately address this question. While recognised case numbers remain very small (4 confirmed, 1 probable, 2 possible), the paucity of information (particularly whether VSBV-1 is a natural infection in certain exotic squirrel species, and the size of the at risk population) precludes an accurate assessment of the wider human health significance. So far, serological testing and case finding has been done to a limited extent, and not all breeders who were approached consented to take part. However, of the 52 squirrel breeders/zoo workers, 9 household members, and 150 blood donors who have been tested to date, a single seropositive individual was found (the squirrel breeder classified as a probable case).^[5, 6]</p> <p>These findings suggest that human exposure to infected squirrels does not consistently result in infection, but all 4 confirmed cases to date have been fatal. Three of these 4, and both possible cases were in individuals with underlying conditions, possibly rendering them more susceptible. However, 2 cases have been in individuals without underlying disease – 1 confirmed fatal case, and 1 probable case who survived.</p>		
viii) Is the disease highly infectious in humans?	No	Satisfactory
<p>There is currently no evidence of human-to-human transmission.</p>		

The **PROBABILITY** of human infection with VSBV-1 in the:
 UK general public – **VERY LOW**
 High risk group – **LOW to MODERATE**

Qualitative assessment of the risk that VSBV-1 presents to the UK population



Step 2: 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.

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?	No	Poor/Satisfactory
<p>There is currently no evidence of human-to-human spread of VSBV-1 but the risk of such spread cannot be stated with certainty at this time as so few human cases have been identified.</p> <p>There is currently insufficient information to enable an accurate description of transmission pathways of VSBV-1, either within or between humans and squirrels. Although human-to-human transmission cannot be conclusively ruled out for the first 3 diagnosed cases (they met on a regular basis), contact with infected squirrels (squirrel trading between the 3 cases was noted) was seen as the most plausible route of infection [2]. For the fourth case, phylogenetic analysis determined that the virus sequence was highly similar to the sequence from the infected squirrel in the zoological collection in which she worked, leading the authors to conclude that transmission occurred from the squirrel to the human contact[5].</p> <p>As is often the case with novel infections, the first known phenotype of VSBV-1 infection in humans was a fatal illness, in this case an encephalitis. As such, it was initially expected that any similar presentation occurring in persons in contact with a confirmed VSBV-1 case would be identified. However, it is now clear that milder disease presentations are possible, as in the case of the seropositive patient retrospectively identified as a probable case. Further clarification of transmission routes, and the possible importance of infected individuals in this process is awaited.</p>		

ii) Is there zoonotic or vector borne spread?	Yes	Good
<p>The 4 confirmed human cases reported to date had regular contact with variegated or Prevost's squirrels before becoming unwell, and for 2 of the cases, infected squirrels were found in their in-contact collections.</p>		
iii) For zoonoses/vector-borne disease is the animal host/vector present in the UK?	Yes	Good
<p>The animal host is only present in a small number of zoological collections and possibly private homes in the UK. Among BIAZA members, there are 15 collections of VSBV-1 implicated squirrel species. The origin of these animals and their VSBV-1 infection status is unknown.</p>		
iv) Is the population susceptible?	Yes	Satisfactory
<p>Limited information is known about the pathogenesis of this virus in humans, although a recent study suggests that T-cell mediated immunopathology is central to fatal human VSBV-1 infection. Only 4 confirmed, 1 probable and 2 possible human cases of infection have been reported to date, while the total number of individuals exposed to infected squirrels is unknown. Of the 7 infections identified to date, 2 were otherwise healthy and 5 had comorbidities. Based on currently available information, individuals with close and frequent contact with infected squirrels and their environments would be at most risk of exposure to VSBV-1. Of the 52 squirrel breeders/zoo workers, 9 household members, and 150 blood donors who have been tested to date, a single seropositive individual was found (a squirrel breeder who was considered a probable case).^[5, 6]</p>		
v) Does it cause severe disease in humans?	Yes	Good
<p>All 4 confirmed cases reported to date died from complications associated with encephalitis, meningoencephalitis or myeloencephalitis. Although in 3 of these cases co-morbidities were reported (hypertension, type 2 diabetes, renal insufficiency, obesity)^[2], the remaining case had no pre-existing medical conditions^[5]. The 2 recently identified possible cases also had fatal encephalitis, and had co-morbidities^[6].</p> <p>It is now known that less severe disease can occur. A single probable case in a squirrel breeder was identified during follow up of breeders, household members and zoo workers.^[6] This case was in a healthy man in his 40s, who had had an illness with fever and prolonged headache and neurological signs in 2004. On testing in 2018, he had anti-VSBV-1 IgG antibodies (IFAT, ELISA and immunoblot) and VSBV-1 specific memory T-cells.</p>		

vi) Would a significant number of people be affected?	No	Satisfactory
<p>Confirmed, probable and possible human cases of VSBV-1 infection have only been observed in 7 individuals who had close and regular contact with variegated or Prevost's squirrels. Among BIAZA members within the UK, there are only 5 collections of Prevost's squirrels and no registered collections of variegated squirrels. There are also 10 collections of Swinhoe's striped squirrels, 1 of the additional species found to be VSBV1 positive in Germany.</p> <p>While it is possible that these and other susceptible squirrel species may also be in private collections in the UK (unregistered with BIAZA), the numbers exposed to these animals is likely to be very small.</p>		
vii) Are effective interventions available?	Yes/possibly	Satisfactory
<p>The route of transmission of VSBV-1 from infected squirrel to human contacts is currently unknown, but thought possible through bites or scratches, or possibly via the intranasal route [2, 5, 7, 10]. Recent research has also implicated a possible role of contaminated faeces [3]. Based on these theories, avoiding direct contact with infected animals and their environments and the use of appropriate PPE may reduce the risk of infection.</p>		

The IMPACT of VSBV-1 on human health in the UK: LOW to MODERATE

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