Human Animal Infections and Risk Surveillance (HAIRS) group

Qualitative assessment of the risk that variegated squirrel Bornavirus presents to the UK population
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Published September 2018
PHE publications
gateway number: 2018393

PHE supports the UN Sustainable Development Goals
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).

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

Risk assessment document management

<table>
<thead>
<tr>
<th>Date of this assessment</th>
<th>24 August 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version</td>
<td>1.0</td>
</tr>
<tr>
<td>Reason for update</td>
<td>In June 2018, the group determined that the zoonotic potential of variegated squirrel bornavirus (VSBV-1) had now been established, and an assessment of the risk the virus presents to the UK population was required.</td>
</tr>
<tr>
<td>Completed by</td>
<td>HAIRS scientific secretariat and members</td>
</tr>
<tr>
<td>Date of previous risk assessment</td>
<td>14 June 2017 (zoonotic potential)</td>
</tr>
<tr>
<td>Date of initial risk assessment</td>
<td>September 2015 (zoonotic potential)</td>
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</tbody>
</table>

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
Qualitative assessment of the risk that VSBV-1 presents to the UK population
## Summary of risk assessment for VSBV-1 and its impact on the UK population

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th>Since initial detection in 2015, variegated squirrel bornavirus (VSBV-1) has been detected in five squirrel species and implicated in four fatal human infections.</th>
</tr>
</thead>
</table>
| **Summary of the assessment** | **Probability** | UK general public: Very low  
High risk group: Low |
| | **Impact** | Very low to Moderate |
| **Level of confidence in assessment of risk** | Satisfactory |
| **Action(s)/Recommendation(s):** | • communicate the outputs of this risk assessment to the British and Irish Association of Zoos and Aquariums so the risk can be communicated to members with implicated squirrel species in their collections  
• continue to monitor scientific literature for detection of VSBV-1 in other squirrel species  
• continue to monitor scientific literature for human illness associated with VSBV-1 |
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 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.*

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>OUTCOME*</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Is this a recognised human disease?</td>
<td>Yes</td>
<td>Good</td>
</tr>
</tbody>
</table>

The Bornavirus genus includes eight host class specific virus species; two of which contain three viruses known to affect mammals – Borna disease virus 1 and 2 (BoDV-1 and BoDV-2) belonging to Mammalian 1 bornavirus, and variegated squirrel bornavirus 1 (VSBV-1) belonging to Mammalian 2 bornavirus (1).

VSBV-1 was first reported in 2015 following reports of the first three human cases who died of encephalitis of unknown aetiology but with similar clinical symptoms in Germany between 2011 and 2013 (2). The natural host and the geographical range of VSBV-1 have not yet been identified. VSBV-1 has been detected in five squirrel species, endemic to South East Asia and Central America, in private and zoological collections in Europe: the variegated squirrel (Sciurus variegatoides), Prevost’s squirrel (Callosciurus prevostii), Finlayson’s squirrel (Callosciurus finlaysonii), Swinhoei’s striped squirrel (Tamiops swinhoei) and the Red-tailed squirrel (Sciurus granatensis) (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 specific screening for VSBV-1.
Four human cases of VSBV-1 infection have been reported in the literature. All four were reported from Germany, in individuals with regular contact with variegated or Prevost's squirrels. The initial three cases (occurring between 2011 and 2013) were men (aged 63, 62 and 72 years) who resided in the state of Saxony-Anhalt, central Germany and all were breeders of variegated squirrels. 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.

VSBV-1 was first detected via metagenomic analysis of brain and other tissues from a variegated squirrel (healthy, accidental death) owned by one of the three fatal cases of acute encephalitis (2). Molecular and immunohistochemical analysis of brain samples from the three deceased patients confirmed the presence of gene sequences identical to sequences found in the genome of the squirrel.

In June 2018, a further fatal human case of VSBV-1 infection was reported in Schleswig-Holstein, northern Germany (5). This individual was a 45-year old German zoo animal handler who 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.

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?  

<table>
<thead>
<tr>
<th></th>
<th>No/Unknown</th>
<th>Satisfactory</th>
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</thead>
<tbody>
<tr>
<td>To date, human cases of VSBV-1 infection have only been reported in Germany.</td>
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</table>

Of the five VSBV-1 implicated squirrel species, only two are present within collections held by British and Irish Association of Zoos and Aquariums (BIAZA) members (Prevost’s squirrel and Swinhoei’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 Swinhoei's striped squirrels, and possibly other exotic squirrel species, are kept in private collections in the UK as pets (e.g., media report, 2008; Defra personal communication).

We are not aware of any BIAZA registered UK collections of either Prevost's squirrels or Swinhoei'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, personal communication). 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?

<table>
<thead>
<tr>
<th>Yes/presumed</th>
<th>Satisfactory</th>
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</table>
| To date, VSBV-1 has been detected in four human cases and in five distinct exotic squirrel species of South American and Asian origin. Since no incidents of human-to-human transmission have been reported, the main route of introduction into the UK with the 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).

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 three months is recommended due to the possibility of intermittent shedding and/or latent infection with stress activated excretion (3).

It should be noted that 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:

(a) VSBV-1 is ubiquitous in the implicated, and possibly other, exotic squirrel species and was introduced into European collections by an imported animal(s)
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(b) 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
(c) an as yet unidentified European reservoir host

<table>
<thead>
<tr>
<th>iv) Are there effective control measures in place to mitigate against these?</th>
<th>No</th>
<th>Satisfactory</th>
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<tbody>
<tr>
<td>There are currently no restrictions on the importation of exotic squirrel species from European countries. Pre-import screening for VSBV-1 may be possible. The Friedrich Loeffler Institute in Germany has developed a test to detect VSBV-1 in mouth swabs and blood samples from squirrels allowing for ante-mortem detection.</td>
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</table>

<table>
<thead>
<tr>
<th>v) Do environmental conditions in the UK support the natural reservoirs/vectors of disease?</th>
<th>Yes</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
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</table>

<table>
<thead>
<tr>
<th>vi) Will there be human exposure?</th>
<th>High risk groups only</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on the 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. 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.</td>
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</table>

All four human cases of VSBV-1 have been reported in individuals with close and frequent contact with variegated or Prevost’s squirrels, and three had underlying co-morbidities. 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). Further seroprevalence studies of zoo workers and other squirrel handlers are currently underway in Germany to provide greater insight into human exposure to VSBV-1 and the risk it presents to human health (5).

<table>
<thead>
<tr>
<th>vii) Are humans highly susceptible?</th>
<th>No</th>
<th>Satisfactory</th>
</tr>
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<tbody>
<tr>
<td>There is currently insufficient information to accurately address this question. Although case numbers are very small, 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 of VSBV-1. Following the latest reported case (45 year old occupational exposure), VSBV-1 screening of 14 other zoo workers, including six</td>
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</table>
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with regular contact with Prevost’s squirrels, was completed. All tested negative (5). This analysis would indicate that human exposure to infected squirrels does not consistently result in infection, but all reported cases to date have been fatal. Ongoing seroprevalence studies will provide further evidence of the risk of exposure to VSBV-1 in those who handle infected squirrels (5).

The **PROBABILITY** of human infection with VSBV-1 in the:

UK general public - Very Low
High risk group - Low
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- **Is this a recognised human disease?**
  - **NO**
  - **YES**

- **Is this a zoonosis or is there zoonotic potential?**
  - **NO**
  - **YES**

- **Is this disease endemic in the UK?**
  - **NO**
  - **YES**

- **Are there routes of introduction into the UK?**
  - **NO**
  - **YES**

- **Are effective control measures in place to mitigate against these?**
  - **NO**
  - **YES**

- **Do environmental conditions in the UK support the natural reservoirs/ vectors of disease?**
  - **NO**
  - **YES**

- **Will there be human exposure?**
  - **NO**
  - **YES**

  - **YES: general population**
  - **YES: high risk groups**

- **Are humans highly susceptible?**
  - **NO**
  - **YES**

- **Is this disease highly infectious in humans?**
  - **NO**
  - **YES**

**Risk Levels**

- **Very Low**
- **Low**
- **Moderate**
- **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.

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.

<table>
<thead>
<tr>
<th>Question</th>
<th>Outcome*</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Is there human-to-human spread?</td>
<td>No</td>
<td>Poor/Satisfactory</td>
</tr>
</tbody>
</table>

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.

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 three diagnosed cases (they met on a regular basis), contact with infected squirrels (squirrel trading between the three cases was noted) was seen as the most plausible route of infection (2). For the latest case, phylogenetic analysis determined that the virus sequence from the human case was highly similar to the sequence from infected squirrel in the zoological collection, leading the authors to conclude that transmission occurred from the squirrel to the human contact (5).

While it is apparent that human infection with VSBV-1 can result in severe and fatal infections, no further cases or evidence of human infection was found despite active case finding and testing of contacts of human cases following the diagnosis of the first cluster of three cases (6) and the latest occupational exposure case (5).

Currently the known phenotype of VSBV-1 infection in humans is a fatal encephalitic illness and it would be expected that any such presentation occurring in a person in contact with a confirmed VSBV-1 case would be identified. However, a
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<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>milder disease presentation may be missed unless widespread serological screening is undertaken. Such a study is currently underway for individuals with contact with implicated squirrel species in Germany (5).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii) Is there zoonotic or vector borne spread?</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>The four human cases reported to date had regular contact with variegated or Prevost’s squirrels before becoming unwell, and for two of the cases, infected squirrels were found in their in-contact collections.</td>
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</tr>
<tr>
<td>iii) For zoonoses/vector-borne disease is the animal host/vector present in the UK?</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iv) Is the population susceptible?</td>
<td>Yes/unknown</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Limited information is known about the pathogenesis of this virus in humans. Only four human cases of infection have been reported and the total number of individuals exposed to infected squirrels is unknown. 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>v) Does it cause severe disease in humans?</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>All four cases reported to date have died from complications associated with encephalitis, meningoencephalitis or myeloencephalitis. Although in three 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). There is currently no evidence to suggest that exposure to VSBV-1 can result in a milder disease presentation.</td>
<td></td>
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</tr>
<tr>
<td>vi) Would a significant number of people be affected?</td>
<td>No</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Human cases of VSBV-1 infection have only been observed in four individuals who had close and regular contact with variegated or Prevost’s squirrels. Among BIAZA members within the UK, there are only five collections of Prevost’s squirrels and no registered collections of variegated squirrels. 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.</td>
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</tbody>
</table>
vii) Are effective interventions available?  

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<thead>
<tr>
<th></th>
<th>Yes/possibly</th>
<th>Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>The route of transmission of VSBV-1 from infected squirrel to human contacts is currently unknown, but thought possible through bites or scratches (2, 5, 6). 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.</td>
<td>Yes/possibly</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>

The **IMPACT** of VSBV-1 on human health in the UK: Very Low to Moderate
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*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. ‘Significant’ is not quantified in the algorithm but has been left open for discussion and definition within the context of the risk being assessed.
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References


