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# Human Animal Infections and Risk Surveillance (HAIRS) group

## Qualitative assessment of the risk that Hantaviruses present 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 (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 and Rural Development for Northern Ireland.

# Qualitative risk assessment for hantavirus in the UK population

| | |
|---|---|
| **Date of this risk assessment:** | 19 January 2016 |
| **Reason for review:** | Although there had been evidence that hantaviruses were present in the UK rodent population, transmission to humans had only been sporadic. A number of new human cases of hantavirus infection acquired in the UK have been diagnosed since 2013 and the data from new seroprevalence studies suggest higher prevalence than previously expected in high risk groups, particularly those with close contact with pet rats. |
| **External expert contributors acknowledged:** | Lorraine McElhinney, APHA |
| **Date of previous risk assessment:** | 8 April 2013 |
| **Date of initial risk assessment:** | 27 November 2006 |

| SUMMARY OF RISK ASSESSMENT FOR HANTAVIRUS IN THE UK POPULATION | |
|---|---|
| **Probability** | Moderate for high risk groups<br>Very low for the general population |
| **Impact** | Low/Moderate |
| **Level of confidence in assessment of risk** | Good |
| **Action(s)/ Recommendation(s):** | Targeted public health advice for high risk groups.<br>The group will continue to monitor and review new evidence as it becomes available. |

**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) Is this a recognised human disease?** | **Yes** | **Overall evidence: Good** |

Two major clinical presentations of hantavirus disease in humans have been recognised: haemorrhagic fever with renal syndrome (HFRS) in Europe and Asia and hantavirus cardiopulmonary syndrome (HCPS) in the Americas (Jonsson *et al*. 2010). The clinical presentation and severity of the disease largely depend on the causative hantavirus serotype. There are more than 40 recognised hantaviruses of which at least 21 are confirmed to be human pathogens (Jonsson *et al*. 2010). The most common are described in Table 1. The majority of hantavirus infections in humans are likely to be asymptomatic or present with mild and non-specific symptoms (fever, headache, blurred vision, gastrointestinal symptoms and back pain) and therefore probably go undiagnosed.

**Table 1. Clinical Features of Common Hantaviruses (Adapted from Hart & Bennett, 1994; Jonsson *et al.* 2010)**

| Serotype | Puumala | Seoul | Hantaan | Sin Nombre |
|---|---|---|---|---|
| Abbreviation | PUUV | SEOV | HTNV | SNV |
| Geographic distribution | Europe, Asia and Americas | Worldwide | China, South Korea, Russia | North America |
| Rodent host | *Clethrionomys glareolus* (bank vole) | *Rattus norvegicus* (brown rat) & *Rattus rattus* (black rat) | *Apodemus agrarius* (striped field mouse) | *Peromyscus maniculatus* (deer mouse) |
| Associated disease | HFRS | HFRS | HFRS | HCPS |
| Severity | Mild | Moderate | Severe | Severe |
| Renal damage | + | + | +++ | ± |
| Liver damage | No | ++ | + | ± |
| Lung damage | No | No | + | +++ |
| Haemorrhage | ± | + | +++ | ± |
| Mortality | 0 | <1% | 5-10% | 40% |

| ii) | **Is this disease endemic in the UK?** | **Yes** | **Overall evidence: Good** |
|---|---|---|---|

Biomes in the UK currently support the host rodents for three types of hantavirus (PUUV, SEOV and Dobrava [DOBV]) which cause mild to severe forms of HFRS. However, evidence of hantavirus infection in UK rodents, collected both from surveys and epidemiological investigations after reports of human cases, has only been found conclusively for SEOV. Evidence of SEOV infection (RNA positivity) has also been found in wild rats in Belgium, France and the Netherlands (Plyusnina *et al* 2012; Dupinay *et al* 2014; Verner-Carlsson *et al* 2015). A novel hantavirus (Tatenale) was detected in a field vole in England (Pounder *et al* 2013).

The UK evidence, summarised in Table 2, does not have a straightforward interpretation, but seems to suggest that pet rat and commercial rat breeding colonies have a much higher prevalence of SEOV infection, when compared to wild populations. This is probably a consequence of the enclosed spaces and communal contact between rodents within such colonies.

**Table 2. Summary of evidence of hantavirus prevalence in rodent populations in the UK**

| | Reference | Region | Rodent species | Prevalence % | (no.) | Serotype(s) | Test |
|---|---|---|---|---|---|---|---|
| Lab rats | Lloyd et al, 1984; Lloyd and Jones, 1986; Shi *et al* 2003 | (Lab rats associated with cluster of lab-acquired infections) | Albino Wistar rats derived from *Rattus norvegicus* | 100 | (9/9) | 'HNTV-like, later confirmed as SEOV | Immuno-fluorescent antibody, virus isolation |
| Wild rodents | McCaughey *et al*, 1996 | County Down, Northern Ireland | *Rattus norvegicus* (brown rats) | 21.6 | (11/51) | HNTV/SEOV | indirect immuno-fluorescent antibody |
| | | | *Apodemus sylvaticus* (wood mice) | 0.03 | (1/31) | HNTV/SEOV | |
| | | | *Mus domesticus* (house mice) | 28.8 | (17/59) | HNTV/SEOV | |
| | Pounder *et al*, 2013 | North-western England | *Rattus norvegicus* (brown rats) | 0 | (0/133) | - | RNA PCR |
| | | | *Apodemus sylvaticus* (wood mice) | 0 | (0/269) | - | |
| | | | *Mus musculus* (house mice) | 0 | (0/50) | - | |
| | | | *Myodes glareolus* (bank vole) | 0 | (0/35) | - | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Microtus agrestis* (field vole) | 13 | (1/8) | Tatenale | |
| | Yanagihara *et al*, 2014 | England | *Talpa europaea* (mole) | 0 | (0/4) | - | RNA PCR |
| | Jameson *et al*, 2013a | Yorkshire & the Humber | *Rattus norvegicus* (brown rats) | 50 | (2/4) | SEOV | RNA PCR |
| | | | *Apodemus sylvaticus* (wood mice) | 0 | (0/5) | - | |
| | | | *Myodes glareolus* (bank vole) | 0 | (0/2) | - | |
| Domesticated rodents | Jameson *et al*, 2013b; unpublished APHA data | Wales / South England (as part of public health investigation) | *Rattus norvegicus* (brown rats) | 100 | (2/2) | SEOV | RNA PCR |
| | | | Rats from a private breeding colony | 33 | (7/21) | SEOV | Blood PCR |
| | | | | 100 | (21/21) | SEOV | SEOVVNA |
| | | | | 81 | (17/21) | SEOV | RNA PCR |
| | Public Health Wales data, 2015; unpublished APHA data | South Wales (as part of public health investigation) | rats from breeding colony 1 with human clinical cases | 67 | (20/30) | SEOV | RNA PCR |
| | | | rats from breeding colony 2 | 48 | (12/25) | SEOV | |
| | | | rats from a rat farm (clinical case in common with household below) | 50 | (15/30) | SEOV | |
| | | | rats from a household with a human clinical case | 33 | (2/6) | SEOV | |

Hantavirus has not been commonly thought of as a diagnosis among humans in the UK. However, since 2012, eleven confirmed symptomatic cases have been reported in individuals with no travel history (Public Health England data). Most (9/11) of these UK-acquired cases were individuals exposed to infected ‘fancy’ [rats that are kept as pets and exhibition animals (National Fancy Rat Society, 2015)] and other pet rats or rats bred to produce feeding material for reptiles. Epidemiological investigations following these cases has variously led to private rat colonies, semi-commercial breeders and commercial ‘rat farms’, in which hantavirus infection was highly prevalent in sampled populations. Links between patients has been found via the rats, by buying/selling, pet-sitting or caretaking and breeding activities. This evidence suggests hantavirus infection is highly prevalent among ‘fancy pet rats’ and other breeding colonies. Further investigations continue to better characterise the extent of the problem in both human and pet

rat populations. Two other UK-acquired confirmed human cases were exposed to wild rats, which in one incident were tested and shown to be positive for SEOV infection (Jameson *et al*. 2013a).

While these UK-acquired human cases have been due to SEOV, there is no clear evidence to date that other European hantaviruses are infecting humans in the UK. This may be due to both ecological and environmental factors. Animal studies have thus far only found a novel hantavirus (Tatenale) in a field vole (Pounder *et al.* 2013), rather than PUUV which is common in voles elsewhere in Europe. Global warming, by leading to a higher food supply for field voles, might increase rodent population densities and provide the opportunity for higher incidence of HFRS in humans. (Bennet *et al* 2010; Roda Gracia *et al* 2015).

| **iii) Will there be human exposure?** | **Yes** | **Overall evidence: Good** |
|---|---|---|

Hantaviruses are transmitted by infected rodents through urine, droppings, or saliva. Humans can contract the disease when they breathe in aerosolised virus, probably carried on dust particles. Transmission can occur when dried materials contaminated by rodent excreta are disturbed and inhaled, directly introduced into broken skin or conjunctiva, or possibly, when ingested in contaminated food or water. Worldwide, persons have also acquired hantavirus infection after being bitten by rodents. A high risk of exposure has been associated with entering or cleaning rodent-infested structures (Zhenqiang *et al*. 2008).

Reports of human seroprevalence rates - a reflection of past exposure to the virus – in the UK vary (McCaughey & Hart, 2000). Table 3 summarises the data on seroprevalence studies on humans in the UK. No studies have yet been performed in ‘general’ pet rat owners.

**Table 3. Results of seroprevalence studies in humans in the UK**

| Reference | Study group | Total number of samples taken | Number of positive samples | Seroprevalence (%) | Test used |
|---|---|---|---|---|---|
| Coleman, 2000 | Farm workers cohort | n/a | n/a | 4.7 | N/S* |
| Lloyd, 1991 | Nature conservancy workers | 122 | 15 | 12.5 | N/S |
| | Sewage and water workers | 96 | 4 | 4.3 | N/S |
| | Farmers | 130 | 28 | 21.5 | N/S |
| | Water sports enthusiasts | 90 | 5 | 5.1 | N/S |
| Public Health England, 2014 | Control group | 300 | 10 | 3.3 | IF ** |
| | Specialist pet “fancy rat” owners | 79 | 26 | 32.9 | IF |
| | Veterinarians | 170 | 3 | 1.8 | IF |

| | | | | |
|---|---|---|---|---|
| Farmers | 120 | 2 | 1.7 | IF |
| Waste water workers | 70 | 2 | 2.8 | IF |
| Pest control workers | 106 | 3 | 2.8 | IF |

*N/S not stated **Immunofluorescence using specific hantavirus antigens (highest titres to SEOV)

Evidence thus points to fancy rat owners as the highest risk group. Nature conservancy workers also seem to be at increased risk. Evidence is contradictory regarding farmers. Veterinarians, waste water workers and pest control workers do not seem to be at an increased risk. There is no information on general rat or reptile owners, who might be at increased risk because of breeding rats or contact with pet and dead feeder rats, respectively. However, investigations around a recent cluster of three cases in Wales (see Table 2) revealed seropositivity without clinical disease in 7/12 persons exposed to the same rats or environments as the cases (Public Health Wales data, 2015). The general population, having little contact with pet rats and wild rats, would not be expected to have a significant exposure to hantavirus infection.

| **iv) Are humans highly susceptible?** | **Yes** | **Overall evidence: Good** |
|---|---|---|

Human infection occurs most commonly through inhalation of infectious aerosolised rodent saliva or excreta. Acquisition of hantavirus from rodents is related to closeness of contact (with rats or their excreta) or risk activities, such as cage cleaning, so for example, pet rat owners are much more likely to be seropositive for hantavirus. The infective dose is presumed to be low. For SNV, which causes HCPS, persons visiting laboratories where infected rodents were housed were infected after only a few minutes of exposure to animal holding areas (Hart & Bennett, 1999).

Data collated from across Europe indicate that there are several thousand cases of hantavirus infection each year, mostly due to PUUV (ECDC, 2014).

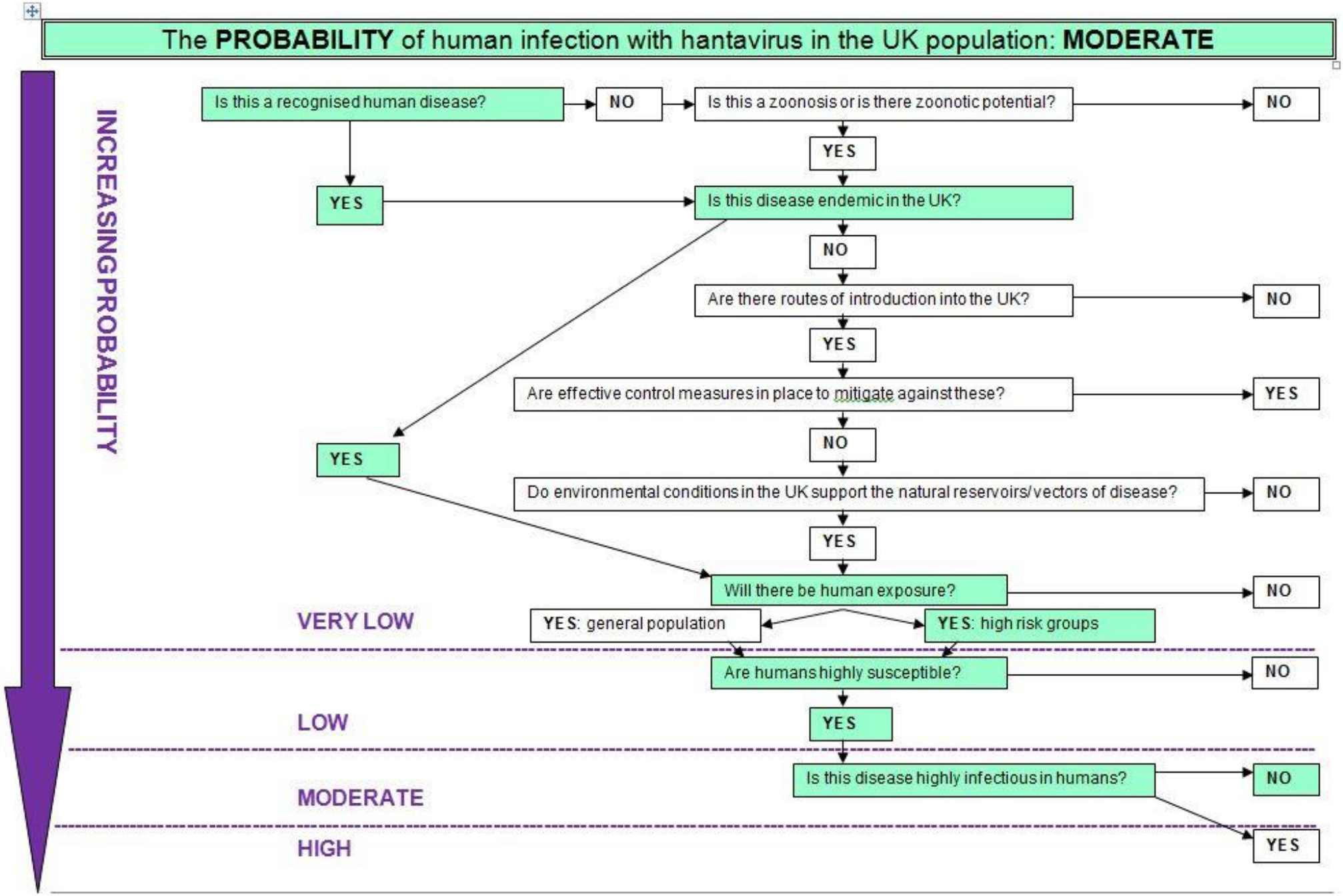
Evidence from a recent seroprevalence study suggests that specialist pet rat owners are commonly exposed to hantavirus, but not the general population or other groups with exposure to wild rodents, such as farmers or pest control workers (Public Health England, 2014; Table 3). At least 100,000 pet rats are kept in an estimated 28,000 households in the UK (PFMA data http://www.pfma.org.uk/pet-population-2014), but the number of diagnosed infections remains small. It is acknowledged however, that cases may well be missed due to lack of awareness amongst clinicians or the mildness of symptoms.

| **v) Is this disease highly infectious in humans?** | **No** | **Overall evidence: Good** |
|---|---|---|

Hantaviruses are transmitted to humans via the inhalation of aerosolised saliva or excreta of infected rodents. The probability of transmission is highly connected to the frequency and intensity of contact, the use of protective equipment and personal hygiene. The infective dose is not known but presumed to be low by analogy with transmission between rodent hosts (infective doses by

aerosol for HTNV, PUUV and SEOV for rodents are 0.5, 0.3 and 0.7 pfu respectively; Nuzum *et al,* 1988) and because persistently infected rodents do not excrete large amounts of virus.

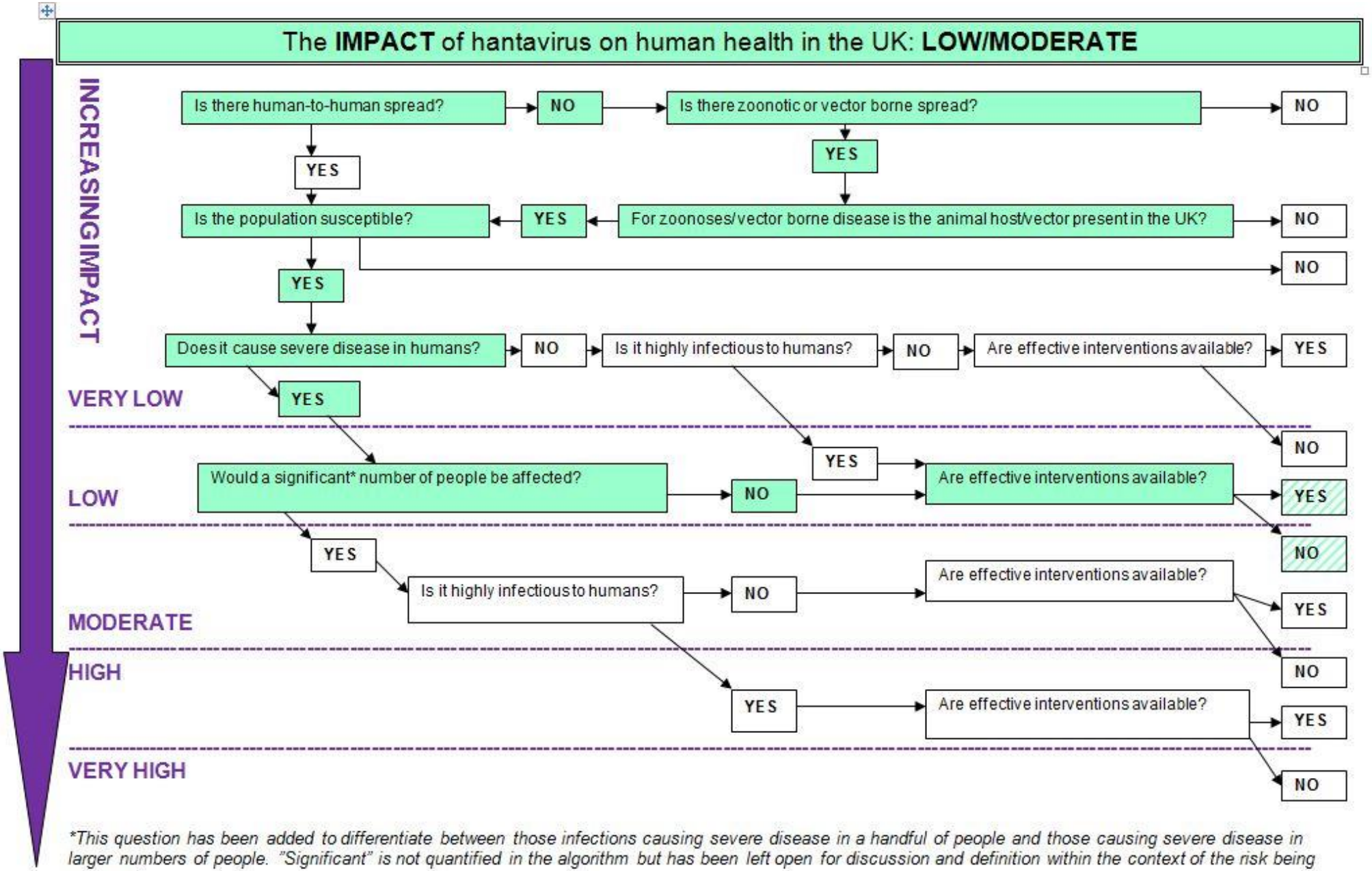
Rodents usually show no sign of infection and, once infected, continue to excrete the virus, possibly for life. Among rodents, the infection is transmitted most commonly between adult animals also through aerosolised virus or, less frequently, through bites and scratches (McCaughey & Hart, 2000). Social behaviour, such as grooming, biting, scratching and exposure to nesting materials are important for the maintenance of the enzootic cycle (Escutenaire & Pastoret, 2000). Recently, the role of mites has been illustrated for transmission of HNTV between field mice (Yu & Tesh, 2014).


The PROBABILITY of human infection with hantavirus in the UK population: MODERATE
INCREASING PROBABILITY
Is this a recognised human disease?
NO
Is this a zoonosis or is there zoonotic potential?
NO
YES
YES
Is this disease 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
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
Is this disease 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 hatching.*

| Question | | Outcome | Quality of Evidence |
|---|---|---|---|
| **i)** | **Is there human-to-human spread?** | **No** | **Overall evidence: Good** |
| Humans are incidental or "dead-end" hosts and there is little evidence to suggest onward transmission. Person-to-person spread has not been associated with hantaviruses in Europe or the United States. However, person-to-person transmission, including nosocomial transmission, has been documented for Andes virus in Argentina (MacNeil *et al*, 2011). | | | |
| **ii)** | **Is there zoonotic or vector borne spread?** | **Yes** | **Overall evidence: Good** |
| Hantaviruses are transmitted mainly by rodents. While a number of other animal species, both wild and domestic, have been found to be infected, there is as yet no evidence to suggest that they are important in transmission to humans. They are most likely to be 'dead-end' hosts, as are humans. (Zeier *et al*, 2005; CFSPH, 2009; Dobly *et al*, 2012). | | | |
| **iii)** | **For zoonoses/vector-borne disease, is the animal host/vector present in the UK?** | **Yes** | **Overall evidence: Good** |
| The rodent vectors for DOB, PUUV and SEOV are present in the UK (Webster & Macdonald, 1995; McCaughey *et al*, 1996; McCaughey & Hart, 2000; Bennett *et al,* 2010). | | | |
| **iv)** | **Is the population susceptible?** | **Yes** | **Overall evidence: Good** |
| Human infection occurs most commonly through inhalation of infectious aerosolised rodent saliva or excreta. Acquisition of hantavirus from rodents is related to closeness of contact, for example pet rat owners are more likely to be seropositive for hantavirus than rural or pest control workers.<br>The infective dose is not known but presumed to be low by analogy with transmission between rodent hosts, and because persistently infected rodents do not excrete large amounts of virus. However, with some hantaviruses subclinical infection is common (up to 20:1), infection occurs more commonly in those aged 20-40 years and is more common in males than females (Hart & Bennett, 1999). | | | |

| | | |
|---|---|---|
| **v) Does it cause severe disease in humans?** | **Yes** | **Overall evidence: Good** |
| Two major human diseases are recognised: HCPS and HFRS. The severity of disease varies with the virus, disease type and human host characteristics. Regarding the most common hantavirus in the UK, SEOV, mortality rates are below 1%. In HFRS, HTNV and DOBV tend to produce the most severe disease, with mortality rates of 5-35%, PUUV is the least severe (<1%) (Jonsson *et al*, 2010; Vaheri *et al*, 2013). HCPS is generally severe with mortality rates of 25-40% (MacNeil *et al*, 2011). Overlap may occur between both syndromes (indistinguishable pathogenesis and clinical presentation) so terms such as "hantavirus disease" have been recently recommended (Clement *et al,* 2012). | | |
| **vi) Would a significant number of people be affected?** | **No** | **Overall evidence: Good** |
| Only people who are exposed to wild, pet or commercial breeding rodents are likely to be affected. Seroprevalence studies suggest that pet rat owners have a particularly high risk, possibly related to the closeness of the contact with the pet (Public Health England, 2014) and people with occupational risk (commercial breeder farms, forestry workers and farmers) might also be at increased risk (McCaughey & Hart, 2000). Data are lacking for SEOV infections, but for PUUV, European case-control studies have identified the main risk factors as proximity to or duration in forested areas, seeing rodents around the home, cleaning little used domestic areas, and contact with wood or disturbed earth or dust (Crowcroft *et al,* 1999; Winter *et al,* 2009; Vaheri *et al,* 2013), | | |
| **vii) Are effective interventions available?** | **Yes/No** | **Overall evidence: Good** |
| There is no specific treatment or cure for hantavirus infection. Preventive measures include avoiding exposure to infected rodents through rodent control, use of personal protective equipment and personal hygiene measures. Once infection occurs, ribavirin is the only specific treatment that has been shown to reduce the case-fatality rate for patients infected with HTNV if given within the first five days of illness, but it is not effective for the treatment of HPS. Treatment is general supportive therapy (Kruger *et al*, 2011; Poliquin *et al,* 2015).<br>Inactivated virus vaccines are used in some countries (eg China and Korea) where they have reduced the incidence of HFRS, however there are no licensed vaccines available in other regions (Schmaljohn 2012; Poliquin *et al*, 2015). One DNA-based vaccine for the PUUV and HTNV viruses has reached phase I clinical trial (Hooper *et al*, 2014). | | |




*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.

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