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## Possible ecology and epidemiology of medically important mosquito-borne arboviruses in Great Britain

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### SUMMARY

Nine different arboviruses are known to be transmitted by, or associated with, mosquitoes in Europe, and several (West Nile, Sindbis and Tahyna viruses) are reported to cause outbreaks of human disease. Although there have been no reported human cases in Great Britain (GB), there have been no published in-depth serological surveys for evidence of human infection. This paper investigates the ecological and entomological factors that could influence or restrict transmission of these viruses in GB, suggesting that in addition to West Nile virus, Sindbis and Tahyna viruses could exist in enzootic cycles, and that certain ecological factors could facilitate transmission to humans. However, the level of transmission is likely to be lower than in endemic foci elsewhere in Europe due to key ecological differences related to spatial and temporal dynamics of putative mosquito vectors and presence of key reservoir hosts. Knowledge of the potential GB-specific disease ecology can aid assessments of risk from mosquito-borne arboviruses.

### INTRODUCTION

There is currently considered to be no transmission of mosquito-borne arboviruses to humans in Great Britain (GB), despite a number of mosquito-borne arboviruses being endemic in other parts of Europe, where they cause human disease. However, to date no in-depth serological surveys for mosquito-borne viruses in the GB human population have been published, and therefore an assessment of their possible ecology and epidemiology is required to aid understanding as to whether these viruses already exist enzootically in GB and whether they could be associated with human infection.

A number of papers have reviewed the known transmission dynamics of mosquito-borne arboviruses

endemic in Europe [1–3], with suggestions that they may occur enzootically in the United Kingdom (UK) [4]. Following the large-scale outbreak of West Nile virus (WNV) in North America and recent outbreaks in Romania, Russia, Israel and France, an investigation into the presence of mosquito-borne viruses in GB was conducted, resulting in evidence of neutralizing antibodies to WNV, Sindbis virus and Usutu virus in British resident birds [5]. Prior to this, the only previous record of a mosquito-borne arbovirus in GB was serological evidence of Tahyna virus in small mammals in Devon [6]. The recent spread of WNV across North America, coupled with seropositivity in British resident birds have led to the development of UK contingency plans for WNV [7] and vector control [8].

The occurrence and abundance of mosquito vector species, or potential vector species, is a prerequisite for enzootic transmission of mosquito-borne viruses in GB. Thirty-three mosquito species have been

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recorded in GB (Table 1): six species of Anophelinae (genus *Anopheles*) and 27 species of Culicinae in seven genera: *Aedes* (2), *Ochlerotatus* (11), *Finlaya* (1), *Coquillettidia* (1), *Culex* (4), *Culiseta* (7), and *Orthopodomyia* (1). Several species (*Ae. vexans*, *An. algeriensis*, *Cx. modestus*, *Cs. longiareolata*, *Cs. alaskaensis*, *Oc. communis*, *Oc. leucomelas*, *Oc. sticticus* and *Or. pulcripalpis*) are either rare, adopt localized distributions or have only historically occurred in GB and can therefore be generally discounted from eco-epidemiological studies of mosquito-borne arbovirus transmission in GB. An ecological understanding of candidate mosquito vectors of arboviruses is an important aspect of surveillance and aids assessment of likely spatio-temporal dynamics of transmission and associated public health risks. A detailed review of the ecology of candidate WNV mosquito vectors in the British Isles based upon known vector status in continental Europe and host preferences of endemic species has been published [9]. The main aims of this paper are to assess the ecological potential for transmission of other mosquito-borne arboviruses in GB and associated public health concerns and secondly, by incorporating data on distribution from the British mosquito recording scheme to identify areas for possible transmission and more importantly targeted surveillance of potentially medically important arboviruses including WNV†.

### Mosquito-borne arboviruses in Europe

Up to 1996, eight arboviruses transmitted by, or associated with, mosquitoes had been recorded in Europe (Table 2; [2]) including: members of the Togaviridae (Sindbis), Flaviviridae (West Nile, dengue), and Bunyaviridae (Batai, Inkoo, Lednice, Tahyna and Uukuniemi); Usutu virus has since been added to this list [13]. Five of these arboviruses are generally associated with human disease in Europe: Sindbis, West Nile, Tahyna, Batai and Inkoo. The public health concerns for GB will now be considered in more depth.

† Although currently available distribution maps do not represent a complete picture of the distribution of British mosquitoes [10], they provide, through the combination of recorded distributions of potential vectors, an insight into areas where transmission might occur and therefore assist in targeting surveillance of arboviral transmission. It should be borne in mind, however, that other areas not illustrated on these maps could be suitable for transmission of these arboviruses and the development of geospatial risk maps would be useful. However, incorporating a number of different mosquito species that favour a variety of diverse ecologies would be complex.

### Sindbis virus (SINV)

SINV (Togaviridae: *Alphavirus*) was first isolated from *Cx. univittatus* near Sindbis village, Egypt in 1952, with the first human case reported in Uganda in 1961. SINV has since been isolated from Africa, Europe, Middle East, Asia and Australia; however, it only appears to be clinically apparent in northern Europe (mainly 60°–64° N) and in South Africa [14]. In Scandinavia, infection with SINV or SIN-like viruses is known by different names in different regions: Ockelbo disease in Sweden, Karelian fever in western Russia, and Pogosta disease in Finland.

There have been no fatal human cases reported and many SIN or SIN-like virus infections are moderate or mild, especially in children and adolescents, so the potential exists for under-reporting and/or under-diagnosis [15]. There appears to be more sub-clinical infections than clinical cases with reported ratios of 20:1 to 40:1 in Sweden and 17:1 in Finland [16, 17]. However, where clinical disease in humans does occur the infection is characterized by fever, rash and arthritis, with non-pruritic skin lesions beginning as macules, which become papular and progress to central vesicle formation, which are, occasionally, haemorrhagic [18]. Arthralgias occur in large and small joints, particularly ankles, wrists and knees [19] and may be so severe as to be immobilizing [20] with moderate joint pain and stiffness persisting for months or years, with chronic joint (or muscle) problems occurring in ~20% of cases [20]. Following the first human case in Sweden in the 1960s, Ockelbo disease was responsible for considerable morbidity in Scandinavia during the 1980s. In 1981, the Russian federation and Finland reported 200 and 300 laboratory-confirmed cases of Karelian fever and Pogosta disease respectively [21]. The largest Pogosta disease outbreak occurred in Finland in 1995 with 400 confirmed cases. Annual incidence rates in endemic regions of affected countries range from 2.7/100 000 in Finland, 2.9/100 000 in Sweden to 18/100 000 in northern Karelia [16, 17]. Epidemics can involve hundreds of people, and in these epidemic years, the number of cases may be 10 times higher than in non-epidemic years. The annual number of cases in Finland from 1980 to 1996 ranged from 1 to 1282 [17]. Human disease normally appears at the end of July or beginning of August, peaks in late August with few cases from October [16].

A virus closely related to SINV (Ockelbo virus) was first isolated from mosquitoes of the genus *Culiseta*

Table 1. Mosquitoes recorded from Great Britain (after [9])

Species	Occurrence [10, 11]	Preferred aquatic habitat in Great Britain	Species	Occurrence [10, 11]	Preferred aquatic habitat in Great Britain
<i>Aedes cinereus</i>	Widespread, patchy	Flooded habitats	<i>Culiseta longiareolata</i>	Very few reports	—
<i>Aedes vexans</i>	Sporadic reports	Temporary pools	<i>Culiseta alaskaensis</i>	Occasional reports in north	—
<i>Anopheles algeriensis</i>	Few reports	—	<i>Culiseta annulata</i>	Widespread	Permanent waters
<i>Anopheles claviger</i>	Widespread	Permanent waters	<i>Culiseta fumipennis</i>	Widespread: E, S and W England	Permanent waters
<i>Anopheles messeae</i> *	Widespread	Permanent waters	<i>Culiseta litorea</i>	Widespread in south	Coastal waters
<i>Anopheles atroparvus</i> *	Widespread	Coastal waters	<i>Culiseta morsitans</i>	Widespread throughout	Permanent waters
<i>Anopheles daciae</i> *	Reported locally	Permanent waters	<i>Culiseta subochrea</i>	Uncommon	Permanent waters
<i>Anopheles plumbeus</i>	Widespread	Tree-holes	<i>Finlaya geniculatus</i>	Widespread in England	Tree-holes
<i>Coquillettidia richiardii</i>	Widespread	Permanent waters	<i>Ochlerotatus annulipes</i>	Widespread	Temporary pools
<i>Culex modestus</i>	Few historical reports	—	<i>Ochlerotatus cantans</i>	Widespread	Woodland pools
<i>Culex pipiens s.s.</i>	Widespread, abundant	Permanent waters	<i>Ochlerotatus caspius</i>	Limited in south	Coastal waters
<i>Culex pipiens</i> biotype <i>molestus</i>	Locally sporadic	Usually underground	<i>Ochlerotatus communis</i>	Few records	—
<i>Culex torrentium</i>	Abundant in S. England	Permanent waters	<i>Ochlerotatus detritus</i>	Widespread, patchy	Coastal waters
<i>Culex europeus</i>	Widespread, few records	Permanent waters	<i>Ochlerotatus dorsalis</i>	Localized	Temporary fresh/brackish pools
<i>Orthopodomyia pulcripalpis</i>	Few records in S. England	Tree-holes	<i>Ochlerotatus flavescens</i>	Localized	Flooded habitats
			<i>Ochlerotatus leucomelas</i>	One report	—
			<i>Ochlerotatus punctor</i>	Widespread	Woodland pools
			<i>Ochlerotatus sticticus</i>	Few historical reports	Temporary pools
			<i>Ochlerotatus rusticus</i>	Widespread	Flooded habitats

\* These three sibling species are members of the *Anopheles maculipennis s.l.* complex.

Table 2. List of recorded mosquito-borne arboviruses in Europe

Arbovirus	Classification	Known distribution [2, 5, 12]
Sindbis (SINV)	Togaviridae <i>Alphavirus</i>	<i>Area:</i> NW and S Russia, Finland, Sweden, Norway, Italy, Slovakia, Hungary, Poland, Estonia <i>Abs:</i> Austria, Serbia, Bulgaria, Czechland, Romania, Moldavia, Ukraine, Belarus, Spain, UK
West Nile (WNV)	Flaviviridae <i>Flavivirus</i>	<i>Area:</i> South Russia, Ukraine, Moldavia, Belarus, Romania, France, Spain, Portugal, Slovakia, Hungary <i>Abs:</i> Czechland, Austria, Italy, Serbia, Croatia, Montenegro, Albania, Greece, Bulgaria, Poland, Bosnia, Turkey, UK
Tahyna (TAHV)	Bunyaviridae <i>Bunyavirus</i>	<i>Area:</i> Slovakia, Czechland, Austria, Hungary, Slovenia, Serbia, Romania, Sweden, France, Italy, Germany, Norway, Estonia, Moldavia, Ukraine, Russia <i>Abs:</i> Poland, Croatia, Bosnia, Lithuania, Finland, Iceland, UK, Spain, Portugal, Albania, Greece
Inkoo (INKV)	Bunyaviridae <i>Bunyavirus</i>	<i>Area:</i> Finland, Sweden, Norway, Estonia, Russia
Batai (BATV)	Bunyaviridae <i>Bunyavirus</i>	<i>Area:</i> Slovakia, Czechland, Austria, Croatia, Serbia, Sweden, Norway, Russia, Moldavia, Ukraine <i>Abs:</i> Finland, Hungary, Bosnia, Montenegro, Italy, Romania, Germany, Portugal
Usutu (USUV)	Flaviviridae <i>Flavivirus</i>	<i>Area:</i> Austria, Hungary <i>Abs:</i> UK
Lednice (LEDV)	Bunyaviridae <i>Bunyavirus</i>	<i>Area:</i> Czechland <i>Abs:</i> Romania
Dengue (DENV)	Flaviviridae <i>Flavivirus</i>	<i>Area:</i> Greece (1927–1928) <i>Abs:</i> Former Yugoslavia

*Area*, Based on virus isolation or autochthonous disease; *Abs*, serological evidence only.

in Sweden in 1982 [22] with SINV/SIN-like viruses isolated from *Cx. pipiens*/*Cx. torrentium*, *Cs. morsitans* and *Ae. cinereus* in Sweden [23], *Aedes/ Ochlerotatus* in Norway and Russia [24, 25], and from *Hyalomma marginatum* ticks in Italy [26]. During studies in Sweden [23], SIN-like virus was only isolated from mosquitoes collected during July and August with highest ‘minimum field infection rates’ (MFIR) reported in August. The monthly MFIR for *Cx. pipiens*/*Cx. torrentium* (5.0/1000 in July, 12.6/1000 in August) was consistently higher than in *Cs. morsitans* (2.0/1000 in July, 4.1/1000 in August), with *Ae. cinereus* exhibiting a MFIR of 0.3/1000 in August. This suggests that *Cx. pipiens* and *Cx. torrentium* are potential enzootic vectors among birds mainly from late spring to mid-summer, with *Cs. morsitans* as a potential additional enzootic vector in late summer [27, 28], and *Ae. cinereus* as a potential bridge vector for transmission from viraemic birds to humans. The relative roles of *pipiens* and *torrentium* as enzootic vectors was investigated by orally infecting both species with a range of doses of virus and after an incubation period testing the mosquito’s ability to

transmit [29]. *Culex torrentium* was highly susceptible to Ockelbo virus by the oral route and transmitted the virus effectively to chickens. One of two mosquitoes that ingested a blood meal containing  $< 10^2$  p.f.u./ml became infected, and all mosquitoes that ingested a blood meal containing  $> 10^4$  p.f.u./ml became infected. All 10 re-feeding *Cx. torrentium* transmitted Ockelbo virus to susceptible chickens. In contrast only one of 28 *Cx. pipiens* was infected after ingestion of a blood meal of  $10^{3.0-3.9}$  p.f.u./ml, with the frequency of infection increasing to 53% after ingestion of  $10^6$  p.f.u./ml. Transmission rates were correlated positively with the virus concentration but were much lower in *pipiens* than *torrentium*, and it seems clear that *Cx. torrentium* is an efficient laboratory vector, and that *Cx. pipiens* was relatively refractory and a poor vector. Similar competence experiments with SINV/SIN-like virus in Swedish *Aedes* species showed that *Ae. cinereus* was relatively susceptible to infection and could transmit the virus [30]. Based on virus occurrence in wild mosquitoes and the results of experimental infection and transmission studies, it is clear that *Cx. torrentium* is the main vector for

Table 3. Basic bionomics of candidate enzootic and human bridge vectors of SINV in Great Britain: vector potential inferred from host preference(s)

Mosquito species	Aquatic habitats	Distribution in Great Britain	Annual generations	Overwintering stage	Preferred hosts	Monthly activity in Great Britain*
<i>Culex torrentium</i>	Permanent waters	Abundant in S. England	Multivoltine	Adults	Birds	L/A (4-11) H (9-4)
<i>Culiseta morsitans</i>	Permanent waters	Widespread throughout	Univoltine	4th instar larva	Mainly birds, some humans	L (9-6) A (4-8)
<i>Aedes cinereus</i>	Flooded habitats	Widespread, patchy	Univoltine	Egg	Mainly cattle, also birds and humans	L (4-6) A (6-8)
<i>Culex pipiens</i> typical form	Permanent waters	Widespread, abundant	Multivoltine	Adults	Birds	L/A (4-11) H (9-4)
<i>Ochlerotatus cantans</i>	Woodland pools	Widespread	Univoltine	Egg	Mainly cattle, also birds and humans	L (1-7) A (4-9)

A, Adults; H, hibernating adults; L, larvae.

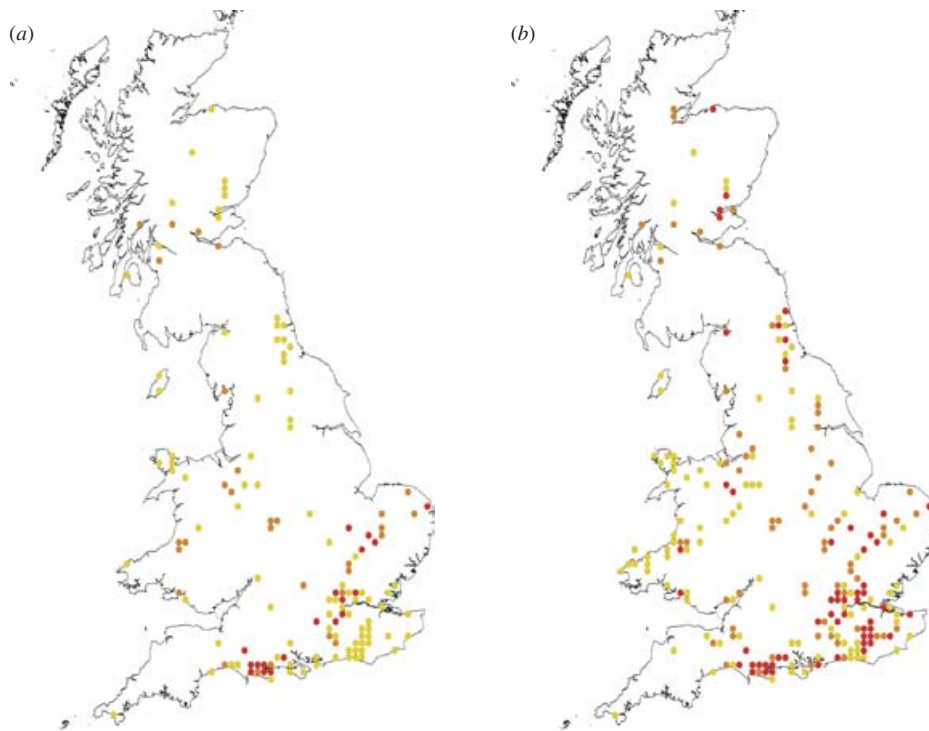
\* Months of activity, from January (1) to December (12), in parentheses.

transmission among birds in Sweden, and that *Ae. cinereus* is the main vector for transmission from viraemic birds to humans [31].

The main enzootic vector *Cx. torrentium* and the potential enzootic mosquito vector *Cs. morsitans* are present and abundant in GB. The potential, but probably not very important enzootic vector *Cx. pipiens* is also present and abundant in GB. The two *Culex* species are almost morphologically indistinguishable, with very few bionomic differences, both being strongly ornithophilic, occupying similar larval habitats such as ponds, marshes, backwaters of streams, hoof prints, pools, ditches and water-containing tree-holes, tanks, butts and discarded tyres [9, 32, 33]. Whilst *Cx. pipiens* (nominant ornithophilic biotype) is widespread across GB, *Cx. torrentium* occurs mainly in southern England, where it predominates over *Cx. pipiens* in peri-domestic habitats. Human biting has rarely been recorded in either species and their roles as bridge vectors is considered negligible. Similarly *Cs. morsitans* is predominantly ornithophilic, and although there is documented evidence of biting of humans [34], this behaviour is considered rare.

Transmission to humans is due to involvement of mosquitoes of the genus *Aedes* with less specialized feeding habits. In Sweden, human infection with SINV appears to occur where enzootic cycles with *Cx. torrentium* exist, and where large numbers of *Ae. cinereus* can facilitate the transmission to humans. *Aedes cinereus* has a widespread but patchy distribution across mainland Britain and, where it is locally common, is a troublesome biter of humans [33]. Aquatic sites include areas prone to freshwater summer flooding with females biting a variety of mammals including humans. Other aedine mosquitoes in GB that might be suggested as potential bridge vectors include *Oc. cantans* and *Oc. communis* [24, 27]. The latter has only been recorded on a few occasions [10] whereas the former is widespread and patchily abundant in woods and scrublands across most of GB. The ecologies of all six mosquito species are detailed in Table 3 and their known distributions are illustrated in Figure 1(a, b).

In Sweden, passeriformes appear to be the principal vertebrate hosts for Ockelbo virus (neutralizing antibodies in 27% passeriformes, 6% galliformes, 4% anseriformes) [35]. In a later study, SINV appeared to infect almost all passerine species with prevalence rates of neutralizing bodies to SINV reported as 6.6% in *Erithacus rubecula* (robin), 12.8% in *Turdus merula*



**Fig. 1.** Reported distribution of candidate mosquito vectors of SINV depicts (a) 10-km grid squares where the most likely candidate enzootic vectors (*Cx. torrentium* and *Cs. morsitans*) and the most likely candidate bridge vector (*Ae. cinereus*) have been reported, (b) additionally incorporates another possible candidate enzootic vector (*Cx. pipiens* typical biotype) and candidate bridge vector (*Oc. cantans*). Red represents bridge and enzootic putative vectors together, orange represents bridge vectors alone, yellow represents enzootic vectors alone.

(blackbird), 4.2% in *Sylvia borin* (garden warbler), 5.8% in *Sylvia atricapilla* (blackcap), 4.3% in *Phylloscopus trochilus* (willow warbler), 1.9% in *Parus major* (great tit), 7.3% in *Fringilla coelebs* (chaffinch), 12.9% in *Carduelis chloris* (greenfinch), 8.7% in *Pyrrhula pyrrhula* (bullfinch) and 1.9% in *Emberiza citronella* (yellowhammer) [36]. The ubiquity of these species and other passerine birds in GB suggests that the lack of reservoir hosts may not be a limiting factor. However, three species of thrush in Sweden reported the highest prevalence rates: 43.3% in *Tu. pilaris* (fieldfare), 22.2% in *Tu. philomelos* (song thrush) and 37.0% in *Tu. iliacus* (redwing), with the conclusion that these three bird species are likely to be the main amplification hosts for SINV in Sweden. The authors concluded that the relative abundance of these three species relative to all other bird species was important in the virus dynamics at a particular site, concluding that the main endemic area for SINV in Europe (i.e. Scandinavia) is closely and positively associated with the abundance of these thrush species. The restricted distribution of clinically apparent disease between 60° N and 64° N may, therefore, be a function of the presence of large numbers of these

virus-amplifying hosts during the summer mosquito season, as well as perhaps a climate restriction of the virus.

In Finland however, 30% of game birds had SINV antibodies in 1981–1983 and during the large epidemic of Pogosta disease in 1981, 65% of *Tetrao* species (black grouse *Tetrao tetrix* and capercaillie *Te. urogallus*) were seropositive. Coupled with the high titres in capercaillie [35] it is postulated [17] that the epidemic years of Pogosta disease every 7th year in Finland are linked to the 6- to 7-year cycle of tetraonid birds and that cycling of the herd immunity among birds causes the 7-year interval of human SINV epidemics in Finland.

The three bird species implicated as main amplification hosts in Sweden occur in GB but unlike Sweden, neither *Tu. pilaris*, nor *Tu. iliacus* breed in GB in any large numbers during the summer months (1–5 and 30–50 breeding pairs respectively [37]). In fact *Tu. pilaris* and *Tu. iliacus* are primarily winter visitors to GB arriving from their Scandinavian breeding sites in large numbers (750 000 birds each) from October onwards. The diversity of passerine hosts present in GB suggest that based purely on

ecology, and provided suitable mosquito species are in abundance, SINV may occur in enzootic cycles. This is supported by serological evidence from GB [5] with the highest seroprevalence in *Tu. merula* (blackbird; 56%,  $n=9$ ), *Corvus corone* (carrion crow; 62%,  $n=26$ ), and *Pica pica* (magpie; 51%,  $n=45$ ), with evidence of SINV-neutralizing antibodies in sera from a further seven wild and domestic birds from GB collected in 2001 and 2002. However, assuming that a similar involvement of thrushes in virus amplification is required in GB, the absence of large numbers of *Tu. pilaris* and *Tu. iliacus* in GB during the summer mosquito season may limit the amplification of the virus in resident birds and hence limit the possibility for large outbreaks of human disease. Where SINV may occur in resident passerines, any subsequent transmission to humans in GB would probably be spatially restricted to areas with large numbers of both *Cx. torrentium* and *Ae. cinereus* mosquitoes, with human cases likely to correlate with the seasonality of the main bridge vector, in July and August (areas where these mosquito vectors do appear to coincide is illustrated in Fig. 1). Regarding the possible involvement of tetraonid birds in virus cycles (as in Finland), neither *Te. tetrix* nor *Te. urogallus* occur in Britain in any significant numbers (both priority conservation species) and it therefore seems that a similar cycle to that seen in Finland occurring in GB is unlikely. Other members of the family Tetraonidae do occur in GB, for example *Lagopus lagopus* (red grouse) is abundant in parts of Scotland, however, there is no evidence linking this species to SINV [17].

### West Nile virus (WNV)

Recent animal and human WNV outbreaks in the Mediterranean basin and the United States are described in detail elsewhere [38–41]. The background to WNV (Flaviviridae: *Flavivirus*) epidemiology and detailed ecologies of candidate enzootic and bridge vectors in relation to the British Isles have also been discussed in detail [9, 42] and reference should be made to these articles. However, a summary table of candidate mosquito species that could be implicated in transmission of WNV in GB is provided in Table 4 and the possible spatial dynamics of transmission based upon known records of mosquito distributions are detailed in Figure 2. Regarding seasonality of transmission to humans, due to the large spectrum of potential mosquito vectors, transmission could

feasibly occur between May and October, however, it is likely to be elevated during the summer months of July, August and early September.

### Tahyna virus (TAHV)

Tahyna virus (Bunyaviridae: *Orthobunyavirus*) belongs to the California complex of bunyaviruses. TAHV was first isolated in 1958 in Slovakia from *Ae. vexans* and *Oc. caspius* [43], and has subsequently been reported from France, Austria, Czechland, Germany, Serbia, Slovenia, Hungary, Romania, Italy, Russia, Ukraine, Moldova and other parts of the former USSR [2, 3, 31, 44], as well in Asia and Africa. Serosurveys of small mammals around Exeter, south-western England [6], found that *Apodemus sylvaticus* (wood mouse) and *Clethrionomys glareolus* (bank vole) had antibodies to TAHV.

According to the World Health Organization [45], TAHV-infected humans may present with influenza-like symptoms, and sometimes as meningoencephalitis and atypical pneumonia. No fatal cases have been reported, and many infections are unapparent, despite high antibody prevalences (60–80%) among inhabitants of endemic foci. Symptomatic cases manifest as an acute influenza-like disease (more common in children) with sudden onset of fever lasting 3–5 days, with headache, malaise, conjunctivitis, pharyngitis, myalgia, nausea, gastrointestinal disorders, anorexia and occasional arthralgia [46]. In Slovakia, every seventieth case of febrile illness in children and every fifth case of CNS illness in children is caused by TAHV [47], and in Czechland every seventh influenza case and every fifth case with manifestations of meningoencephalitis in the summer months can be ascribed to this virus [48]. WHO states that ‘inasmuch that TAHV is widespread in Europe and may cause severe disease, it must be considered of public health importance at present, bearing in mind its even greater potential for increased incidence, especially as its vectors are so widespread’ [45].

TAHV vectors are mainly pasture-breeding species of the genera *Aedes* and *Ochlerotatus*, with TAHV isolated from several species of mosquito including *Ae. vexans*, *Oc. caspius* (*caspius/dorsalis*), *Ae. cinereus*, *Oc. cantans* (*cantans/annulipes*), *Oc. sticticus*, *Cs. annulata*, *Cx. modestus*, *Oc. flavescens*, *Coquillettidia richiardii*, *An. maculipennis*, and *Cx. pipiens* [31, 46] with the most virus isolations from *Ae. vexans*, *Oc. caspius/dorsalis*, *Oc. cantans/annulipes* and *Ae. cinereus* [31]. *Aedes vexans* is considered to be the

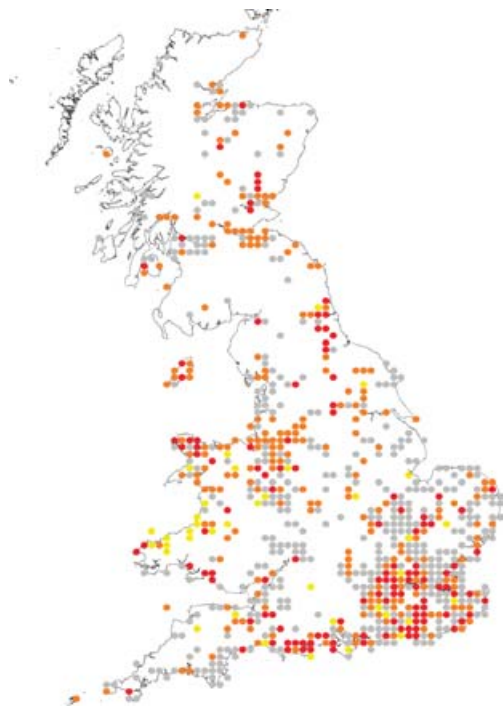
Table 4. Basic bionomics of candidate enzootic and human bridge vectors of WNV in Great Britain: vector potential inferred from host preference(s) (after [9])

Mosquito species	Aquatic habitats	Distribution in Great Britain	Annual generations	Overwintering stage	Preferred hosts	Monthly activity in Great Britain*	Enzootic (E) or bridge (B) vector
<i>Aedes cinereus</i>	Flooded habitats	Widespread, patchy	Univoltine	Egg	Mainly cattle, also birds	L (4–6) A (6–8)	B
<i>Ochlerotatus cantans</i>	Woodland pools	Widespread	Univoltine	Egg	Mainly cattle, also birds and humans	L (1–7) A (4–9)	B
<i>Ochlerotatus detritus</i>	Coastal waters	Widespread, patchy	Multivoltine	4th instar larva	Mainly cattle and humans, some birds	L (1–12) A (3–11)	B
<i>Ochlerotatus punctor</i>	Woodland pools	Widespread	Univoltine	Eggs and larvae	Mainly cattle, some humans and birds	L (11–8) A (4–10)	B
<i>Anopheles plumbeus</i>	Tree-holes	Widespread	Bivoltine	4th instar larva	Mammals, incl. humans	L (1–12) A (4–10)	B
<i>Coquillettidia richiardii</i>	Permanent waters	Widespread	Univoltine	Larvae	Cattle, humans and birds	L (1–12) A (5–9)	B
<i>Culex pipiens</i> typical form	Permanent waters	Widespread, abundant	Multivoltine	Adults	Birds	LA (4–11) H (9–4)	E
<i>Culex pipiens</i> biotype <i>molestus</i>	Usually underground	Locally sporadic	Multivoltine	All stages	Humans (possibly birds)	LA (1–12)	Possible B
<i>Culex torrentium</i>	Permanent waters	Abundant in S. England	Multivoltine	Adults	Birds	LA (4–11) H (9–4)	E
<i>Culiseta annulata</i>	Permanent waters	Widespread	Multivoltine	All stages	Birds and humans	LA (1–12) H (9–4)	B
<i>Culiseta litorea</i>	Coastal waters	Widespread in south	Univoltine	4th instar larva	Mainly birds, some humans	L (1–12) A (5–9)	E and B
<i>Culiseta morsitans</i>	Permanent waters	Widespread throughout	Univoltine	4th instar larva	Mainly birds, some humans	L (9–6) A (4–8)	E and B

A, Adults; H, hibernating adults; L, larvae.

\* Months of activity, from January (1) to December (12), in parentheses.





**Fig. 2.** Reported distribution of candidate mosquito vectors of WNV: depicts probable areas, based upon known historical distributions of key mosquito species, of candidate enzootic and human bridge vectors of WNV. Red represents areas where both candidate bridge and enzootic mosquito vectors have been recorded together in the same 10-km grid (most probable areas for human transmission), orange represents where candidate bridge vectors occur alone (where transmission to humans might occur but possibly at a lower rate, bridge vectors may also act as enzootic vectors, but in general, they are not classically ornithophilic), and yellow represents where candidate enzootic vectors occur alone. All grid locations represented in grey show the reported distribution of all other mosquito species which although unlikely to be involved in transmission, are included to illustrate coverage of all mosquito distribution data in the database [10].

most important TAHV vector with 58% of all virus isolations resulting from this species. In Europe it is generally considered that *Ae. vexans* seems to be a prerequisite for the maintenance of TAHV transmission cycles in an area. However, although the high number of TAHV isolates in Slovakia were from *Ae. vexans*, this is in contrast to the lack of isolates from this species in Austria where a high number of isolates from *Oc. caspius/dorsalis* indicates that strains of TAHV may utilize different vector species in different geographical locations. Other *Aedes/Ochlerotatus* species clearly do contribute to transmission, and *Culiseta* mosquitoes may be important in the overwintering of TAHV [46], with

transovarial transmission occurring in most of these species [49].

All the mosquito species listed above have been recorded in GB, however, the limited number of records of *Oc. sticticus* and *Cx. modestus* suggest that neither of these species would contribute significantly to transmission of the virus in GB. Additionally, the rare occurrence of *Ae. vexans* in GB may, in line with suggestions over its requirement as a prerequisite for TAHV transmission (see above), suggest that TAHV is likely to be less prevalent in Britain compared to other countries where this mosquito species is abundant and is the main vector. However, the isolation of TAHV from other *Aedes/Ochlerotatus* species including GB resident species and their role as bridge vectors in Europe in place of *Ae. vexans*, imply that five species could be considered as potential bridge vectors of TAHV in GB. They are *Oc. caspius/Oc. dorsalis* (coastal saltwater aquatic sites), *Oc. cantans*, *Ae. cinereus* and *Oc. annulipes* (temporary freshwater pools in flooded meadows and woodland pools). Furthermore all are generally widespread (Table 5, Fig. 3), exhibiting preferences for mammal and human biting (*Ae. cinereus* feeds on mammals including rabbits, and *Oc. cantans* feeds on woodland animals and rabbits).

The most important vertebrate amplifying hosts of TAHV in central Europe appear to be *Lepus europaeus* (brown hare) and *Oryctolagus cuniculus* (European rabbit) [50–52]; both common in GB, the latter abundantly so. Both are considered highly susceptible to TAHV, developing sufficiently high and long-lasting viraemias to infect vectors and are also abundant and attractive hosts for mosquitoes. In addition to *L. europaeus* and *Or. cuniculus*, TAHV produced viraemia in almost all mammal species tested [31] including common British mammals *Erinaceus europaeus* (hedgehog), *Vulpes vulpes* (red fox) and *Meles meles* (badger), more restricted British species *Mustela putorius* (polecat) and *Glis glis* (fat dormouse), and other non-British wild mammals *Cricetus* sp. (hamster), *Citellus citellus* (suslik) and *Martes fiona* (stone marten). TAHV appears incapable of producing viraemias in bats [53], birds [54, 55], amphibians or reptiles [56].

A number of factors including the occurrence of putative mosquito vectors in GB, the abundance of vertebrate hosts that might sustain viraemias to permit transmission, the reports of TAHV in small mammals in Devon, and public health concerns in other European countries, suggest that further

Table 5. Basic bionomics of candidate human bridge vectors of TAHV in Great Britain: vector potential inferred from host-preference(s)

Mosquito species	Aquatic habitats	Distribution in Great Britain	Annual generations	Overwintering stage	Preferred hosts	Monthly activity in Great Britain*
<i>Aedes cinereus</i>	Flooded habitats	Widespread, patchy	Univoltine	Egg	Cattle, mammals, birds and humans	L (4-6) A (6-8)
<i>Ochlerotatus cantans</i>	Woodland pools	Widespread	Univoltine	Egg	Cattle, woodland mammals, rabbits, birds and humans	L (1-7) A (4-9)
<i>Ochlerotatus caspius</i>	Coastal waters	Limited in south	Multivoltine	Egg	Humans, sheep and cattle	LA (4-10)
<i>Ochlerotatus dorsalis</i>	Coastal waters	Localized	Multivoltine	Egg	Cattle	A (5-9)
<i>Ochlerotatus annulipes</i>	Temporary pools	Widespread	Univoltine	Egg	Humans and other mammals	A (4-9)
<i>Culiseta annulata</i>	Permanent waters	Widespread	Univoltine	4th instar	Animals, birds and humans	LA (1-12) H (9-4)

There have been sporadic reports of *Aedes vexans*, and few historical reports of *Oc. sticticus* and *Cx. modestus*.

A, Adults; H, hibernating adults; L, larvae.

\* Months of activity, from January (1) to December (12), in parentheses.



Fig. 3. Reported distribution of candidate mosquito vectors of TAHV. Includes reported distribution of all candidate mosquito vectors of TAHV: *Ae. vexans* is represented by black dots, as this is considered, in Europe, to be the principal vector. All other species (*Oc. cantans*, *Oc. caspius*, *Ae. cinereus*, *Oc. dorsalis*, *Oc. annulipes* and *Cs. annulata*) are represented in grey.

investigation into the potential occurrence, distribution and prevalence of TAHV in GB is required. Furthermore, many of the mosquito species implicated and many of the TAHV outbreaks reported elsewhere in Europe have followed widespread flooding events [57]. The predictions of climate change scenarios suggest wetter milder winters, more frequent storms and flooding in autumn, and although summers are expected to be drier, rainfall is likely to be heavy when it does occur leading to flash flooding. The effect that these predicted weather events might have on endemic mosquito species needs to be considered [58], as well as a greater understanding of the status of *Ae. vexans* in Britain.

**Inkoo virus (INKV)**

Inkoo virus (Bunyaviridae: *Bunyavirus*), a member of the California (CAL) serogroup, is distributed across northern Europe (Norway, Sweden, Finland, Estonia, Russia). Despite neutralization test (NT) antibody surveys in humans showing high prevalences in

northern Sweden (84%) and Finland (Lapland 69%), which suggest that INKV is endemic in Scandinavia (prevalence rates are lower in southern Sweden, 26%, and southern Finland, 15%), there has been no clinical evidence of human disease from INKV in either country. In Russia however, CAL viruses (including INKV) produce significant morbidity (involving neurological disease), and the same situation should be considered in western Europe [3, 45].

INKV was first isolated from a pool of *Oc. communis/punctor* in Finland [59]. In Sweden, INKV has been isolated from both *Oc. communis* [23] and *Oc. punctor* [35], and in Norway there have been isolations from *Oc. communis* and *Oc. sticticus* [60]. Following studies in Scandinavia, it was concluded [3, 23, 35, 60] that the main vector for INKV is *Oc. communis*, although *Oc. punctor* may replace it as a vector in the far north.

*Ochlerotatus punctor*, *Oc. communis* and *Oc. sticticus* have all been reported in GB, with *Oc. punctor* widely distributed from southern England to northern Scotland, with only two records of *Oc. communis* (from Nottinghamshire and Jersey [33]) and only a few widely distributed records of *Oc. sticticus* (from the New Forest to Scotland [32]). *Ochlerotatus punctor* is a woodland mosquito, exhibiting a univoltine life cycle, with adults active between May and October biting predominantly mammals, including cattle and humans. Biting of humans may be fierce and persistent.

Little information is available on vertebrate INKV hosts. However, seroprevalence rates of INKV NT antibodies have been recorded in northern Finland [59] for bovinds (88% in north, 35% in south) and other domestic mammals (89% in north, 31% in south). In other mammals, seroprevalence rates were 89% in *Rangifer tarandi* (reindeer) and 64% in *Alces alces* (moose) – both absent or rare in GB – 37% in *V. vulpes* (red fox) and 5% in *L. timidus* (snow/mountain hare) – both present in GB, the former abundantly so – with no antibodies found in *L. europaeus* (brown hare), or various species of vole (*Microtus agrestis*, *Microtus arvalis*, *Cl. glareolus*), mouse (*Ap. flavicollis*, *Mus musculus*) or bat (*Myotis mystacinus*, *Myotis daubentoni*). In birds INKV NT antibodies were recorded in 0.9% of *Bonasia bonasia* (hazel grouse), but not in *Te. urogallus* (capercaillie), *Te. tetrix* (black grouse) or 13 passerine species tested.

It seems unlikely on current information, that INKV poses a significant risk to human health in

GB. The scarcity of human clinical infections in Scandinavia and the seemingly restricted geographical distribution and preference for northerly latitudes may reduce the likelihood of transmission in GB. However, evidence of significant morbidity in Russia from CAL viruses (including INKV) needs to be considered.

### Batai virus (BATV)

Batai virus (Bunyaviridae: *Orthobunyavirus*) was first isolated in Europe from *An. maculipennis s.l.* as Calovo virus (CVOV) in a village near Calovo, south Slovakia in 1960 [61]. BATV, or closely related viruses, have been identified from several countries in Eurasia and Africa [2], with isolations from Norway, Sweden, Finland, Russia, Ukraine, Czechland, Slovakia, Austria, Hungary, Portugal and Romania, from a number of western European mosquitoes – principally zoophilic *An. maculipennis s.l.* and *An. claviger* with isolations also from *Oc. communis*, *Oc. punctor*, *Ae. vexans* and *Cq. richiardii* [2, 23, 31].

The prevalence of haemagglutination inhibition (HI) antibody to BATV/CVOV in wild and domestic (bovine and ovine) animals ranges from 1% to 46% in studies carried out in Finland, Austria, Slovakia, Portugal, Romania and the former Yugoslavia. Human HI antibody prevalence is generally very low, <1% in Sweden, Finland, Germany, Austria and parts of the former Yugoslavia, with 32% reported in southern Slovakia [3]. Infection with BATV is not generally associated with human disease in western Europe. However, febrile disease, bronchopneumonia, exudative pleurisy, catarrhal and follicular tonsillitis, and acute gastritis have been recorded as clinical signs of BATV infection in the former Czechoslovakia [62]. BATV appears to occur only epidemically in Scandinavia where during an epizootic in the 1960s, neutralizing antibodies were detected in a number of cows and one farmer on coastal farms in Finland where *An. maculipennis s.l.* was common [63, 64]. Clearly BATV is circulating in western Europe, but due to the very low BATV antibody prevalence in humans, in contrast to the high prevalence of antibodies in other mammals, humans are only rarely involved [3]. This, coupled with the mild clinical signs on the occasions where symptoms have been described, suggests that based on current evidence, BATV is unlikely to constitute a significant public health problem for GB.

### Usutu virus (USUV)

Usutu virus (Flaviviridae: *Flavivirus*) is closely related to important human pathogens such as Japanese encephalitis, Murray Valley encephalitis, dengue, yellow fever, St. Louis encephalitis and WNV. It was first isolated from mosquitoes in South Africa in 1959. Prior to 2001 only two isolations had been reported from mammals, one from *Praomys* sp. (African soft-furred rat) and one from a man with fever and rash [5]. USUV had not, until recently, been associated with severe or fatal disease in animals or humans, and it had never before been observed outside tropical or subtropical Africa.

However, from August to mid-September 2001, a considerable die-off of *Tu. merula* (blackbird) was observed around Vienna in Austria and USUV was detected as the cause [12]. Infection was also reported in *Strix nebulosa* (great grey owl), *Hirundo rustica* (barn swallow), *Passer domesticus* (house sparrow) and *Parus caeruleus* (blue tit) – all abundant in GB except *S. nebulosa*. USUV was detected in mosquitoes collected in the area, indicating that USUV has established effective transmission cycles between local mosquitoes and birds. The following year the virus re-appeared, confirming fears that the virus could overwinter in Austria, with USUV now having spread to other parts of Austria and to neighbouring Hungary.

However, after the first 2 years of USUV transmission in Austria there had been no evidence of pathogenicity of the Austrian USUV strain for mammals, including humans. In addition there have been no cases of unclear illness including meningo-encephalitis in domestic animals or in humans in the endemic areas [12]. Evidence [5] of virus-specific neutralizing antibodies to USUV in British birds suggests that it is being introduced here; however, there have been no significant bird die-offs reported. The lack of pathogenicity of USUV for humans suggests that the risk posed by this virus to humans is very low. However, the concern that closely related flaviviruses have been responsible for large-scale human outbreaks elsewhere suggest that a close watch on the status of this virus or closely related viruses in Europe is required. There is limited information on potential vectors, however, USUV viral RNA has been retrieved by RT-PCR from *Cx. pipiens* (the main vector), *Ae. vexans* and *Cs. annulata* (H. Weissenböck, personal communication). *Aedes vexans* is rare in GB, the typical biotype of *Cx. pipiens*

is almost exclusively ornithophilic, however, *Cs. annulata* is a nuisance human-biting mosquito, and has the longest biting season of any British mosquito, responsible for much of the biting reported during late autumn and early spring. It also adopts a wide range of synanthropic natural and artificial aquatic habitats (ponds, ditches, marshes, cisterns and water butts) [32].

### Other arboviruses recorded in Europe transmitted by, or isolated from, mosquitoes

Dengue virus (DENV; Flaviviridae: *Flavivirus*) is not currently endemic to Europe, recorded only historically in Greece where it caused high human mortality in Athens in 1927–1928 [2, 45]. Dengue antibodies have also been recorded sporadically in the former Yugoslavia [44], Spain [65] and Turkey [66], possibly as imported infections. The main vector responsible for DENV transmission globally is *Ae. aegypti*, which no longer occurs in Europe and does not survive in the British Isles [32]. However, *Ae. albopictus*, which is considered to transmit DENV [67] has, over the last 20 years, become established in parts of southern Europe, with records from Albania, Italy, France, Montenegro, Switzerland, Spain, Belgium, Holland, Israel and Greece [68]. There have so far been no reports of transmission of viruses to humans by this mosquito in Europe [67], however, its importation and establishment in GB is a possibility [68, 69]. Despite importations of DENV into GB by infected travellers, the current absence of suitable mosquito vectors and the current climatic constraints (~17 °C is a constraining temperature threshold for development [70]) are generally considered as factors limiting transmission in northern latitudes.

Lednice virus (LEDV; Bunyaviridae: *Bunyavirus*) originally classified as Yaba-1 virus, has only been isolated in Moravia, Czechland [3, 71] from *Cx. modestus* [72]. Antibodies to LEDV have only been reported in waterfowl (including birds common to GB: mallard *Anas platyrhynchos*, greylag goose *Anser anser*, garganey *Anas querquedula*, teal *Anas crecca*, gadwall *Anas strepera* and coot *Fulica atra*) from Czechland and Romania [3, 73]. There have been no reports of human infection, with serological surveys in both locations eliciting no antibodies to LEDV. The lack of human disease, the presence only of antibodies to LEDV in some migratory birds [73] and the probable absence of key mosquito vectors in GB

suggest that LEDV is not currently a public health concern.

Uukuniemi virus (UUKV; Bunyaviridae: *Uukuvirus*) has a wide distribution across northern and central Europe, transmitted primarily by ticks between forest rodents (including mammals *Cl. glareolus*, *Ap. flavicollis* resident to GB) and various ground-feeding passerines. UUKV has been isolated occasionally from various mosquito species (*Cx. modestus*, *Ae. vexans*, *Oc. punctor* and *Oc. communis* [2]) with only *Oc. punctor* common in GB. Human disease from UUKV is rare, with only three cases having been reported from southern Russia [74] and therefore public health implications are considered negligible, however, UUKV has been isolated in GB from *Ixodes uriae* in coastal Scotland [75].

Mosquitoes may also transmit two additional European arboviruses (Sedlec and African horsesickness), with no evidence, however, of human disease [2]. Sedlec virus (SEDV; Bunyaviridae), isolated from warblers and antibodies to it found in a number of reedbelt passerines in Czechland, is possibly transmitted by ornithophilic mosquitoes like *Cx. modestus*, and African horsesickness virus (AHSV; Reoviridae), is occasionally transmitted by *Aedes* and *Culex*, with no records of human disease [2].

## DISCUSSION

Nine different mosquito-borne arboviruses are known to be transmitted by, or associated with, mosquitoes in Europe. However, for many our knowledge of the ecology and distribution of these viruses is limited, and for others the occurrence of human infection or human disease is currently considered rare. In the absence of in-depth studies into the epidemiology of these viruses in other parts of Europe, including GB, it may be premature to discount all these viruses from the public health agenda. Indeed, based upon current and growing evidence, a number of arboviruses are known to infect humans and cause disease, and with serological evidence of SINV, WNV, USUV and TAHV in British resident birds and mammals, the possible public health implications of these and similar viruses need to be continually appraised.

Having considered the ecology and epidemiology of each virus in Europe and the possible dynamics in GB, three viruses (WNV, SINV and TAHV) could, based purely on their ecology, occur in enzootic cycles in GB with the potential for human

involvement. However, the degree to which this might occur, in comparison to other parts of Europe, is likely to be low. The potential ecology of WNV in GB has not been covered in depth here since it has already been considered in much greater detail elsewhere [9].

Regarding SINV, GB is home to all the key enzootic (*Cx. torrentium*, *Cs. morsitans* and *Cx. pipiens*) and bridge (*Ae. cinereus*) vector mosquito species that have been implicated in transmission in northern Europe, and to many of the passerine bird hosts for which the virus has been reported. Amplification of the virus in northern Europe appears to be associated with certain bird species and the occurrence and dynamics of these birds appear to correlate with significant outbreaks of Ockelbo disease in Sweden and Pogosta disease in Finland. In Sweden, fledglings of three thrush species are important in amplifying the virus and in the presence of the key mosquito species are associated with the spatio-temporal dynamics of human infection. Two of these species (*Tu. pilaris* and *Tu. iliacus*), however, do not regularly occur in GB during the summer breeding season (when fledgling numbers are high) and when mosquitoes are abundant, and it is not until the autumn that these two species visit GB. In Finland, the epidemic years of Pogosta disease appear to be related to cycles in tetraonid birds, and whilst members of the Tetraonidae occur in GB, the species implicated in Finland (*Te. urogallus* and *Te. tetrix*) occur in GB in very low numbers. The absence of the two sets of specific eco-epidemiological circumstances described above suggest that, unless an alternative scenario exists to amplify the virus, this may be a limiting factor for large-scale SINV infection in humans in GB. Nevertheless, the possible occurrence of human infection should not be discounted.

TAHV has been reported from a variety of wild mammals with the main amplifying hosts appearing to be *L. europaeus* and *Or. cuniculus*, both of which occur in GB, the latter abundantly. The virus is transmitted enzootically and to humans by a number of *Aedes* and *Ochlerotatus* species, and in some parts of Europe the presence of *Ae. vexans* is a prerequisite for TAHV transmission. However, in other parts of Europe different *Aedes/Ochlerotatus* species appear important, suggesting that different strains of virus might utilize different vector species. *Aedes vexans* is not common in GB, however, the presence of five other candidate *Aedes/Ochlerotatus* vector species (*Oc. caspius*, *Oc. dorsalis*, *Oc. cantans*, *Ae. cinereus*

and *Oc. annulipes*) in GB suggest that TAHV could occur enzootically with possible human involvement.

Determining whether or not any of these viruses, or similar viruses that are discovered, with appropriate eco-epidemiological requirements, occur enzootically or are associated with human infection is clearly reliant upon further field and epidemiological studies. In addition, developing an understanding of the possible ecology and epidemiology of such transmission is dependent upon continued research into British mosquitoes and the development and establishment of databases, organized through the United Kingdom Mosquito Association, on the distribution and abundance of our endemic mosquito fauna. Furthermore, whilst mosquito-borne arboviruses have been isolated from mosquito species in Europe, the ability for British mosquitoes to transmit many of these viruses should be a focus of future research. Isolation of virus from mosquitoes alone is not necessarily evidence of vector status (e.g. Tyulenyi virus), as many mosquito species could become infected with almost any mosquito-borne virus if feeding on a viraemic animal with a high titre viraemia, and therefore the criteria† for incriminating a species as a vector of arboviruses should be considered.

Finally, whilst this paper deals specifically with mosquito-borne arboviruses endemic, or previously endemic, in Europe, the possibility exists for non-European viruses to become introduced. This may occur through movement of infected humans and animals leading to subsequent transmission (e.g. WNV in the United States, USUV in Europe), or as a result of climate change that may promote the abundance and range of endemic or exotic mosquitoes [76] or exotic viruses [4]. The large-scale outbreak of chikungunya virus in the Indian Ocean islands since 2005, and subsequent importation of large numbers of cases into Europe, particularly France [77, 78], raises questions as to whether such exotic viruses could establish in Europe or be transmitted during warmer summers by endemic mosquitoes or by exotic species such as *Ae. albopictus*.

† The criteria for incriminating a species as a vector of arboviruses must all be met for proven vectorial ability: (1) isolation of a specific virus from specimens collected in nature; (2) demonstration of infection in the mosquito following an experimental feeding on a viraemic host or virus suspension; (3) demonstration of transmission of virus by bite to a vertebrate host or demonstration of virus in expressed salivary fluids; (4) field evidence confirming association of the mosquito species with the vertebrate population in which the virus infection is occurring.

An awareness of the possibility for European transmission of 'exotic' viruses by mosquitoes is required, as is a greater understanding of our endemic mosquito fauna, their roles as vectors, as well as the potential for establishment and seasonal activity of exotic mosquito species and the ecological and environmental constraints on the transmission of newly introduced exotic arboviruses.

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## DECLARATION OF INTEREST

None.

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