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# The mosquito-borne infections of Europe

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## Abstract

The number of endemic mosquito-borne infections in Europe is substantial; some, such as West Nile virus give rise to periodic epidemic outbreaks while others cause only sporadic clinical cases of disease. Overall, there is a rising trend in the number of infections, especially of the arboviruses. Malaria which had been eradicated in Europe by 1975 following the initiation of the WHO eradication campaign, is reappearing in epidemic form in some countries of Eastern Europe and the appearance of sporadic autochthonous cases in western European countries is increasing. New mosquito-borne diseases are appearing in Europe, some of them introduced from endemic countries while others are emerging diseases not previously known to occur on the continent of Europe. Public health authorities and clinicians must be aware of the presence of these infections to ensure accurate diagnosis and treatment of individual cases, or prepare surveillance and control measures should outbreaks occur.

## Introduction

Reviews of the status of a number of disease groups such as the arboviruses (Hubalek & Halouzka, 1996; Lundstrom, 1999) and individual diseases such as malaria (Sabatinelli *et al.,* 2001) are available for Europe but overall reviews of the mosquito-borne diseases in Europe are difficult to find. The present article will briefly review the mosquito-borne infectious agents either endemic or introduced into Europe, their distribution and the magnitude of their public health importance.

## Arboviruses

Of the 500 or more known arboviruses, at least 51 have been reported from Europe (Hubalek & Halouzka, 1996). These authors also provided distribution maps of the arboviruses known in Europe at that time. Some of these viruses are not known to cause human illness; while some have been isolated only from arthropods, birds or animals, and their public health significance is unknown. Others may cause significant human illness. Other arboviruses have been recently discovered or introduced into Europe. Only those viruses that are known to be of some clinical importance will be considered below.

### *Togoviridae-Alphaviruses*

### Sindbis virus

Many strains of the Sindbis group of arboviruses are widely distributed throughout Europe. The virus is maintained in nature in a mosquito-bird transmission cycle and is transmitted throughout Europe by migratory birds, with ornithophilic *Culex* species and *Culiseta morsitans* as vectors (Lundstrom *et al.,* 2001). The virus has been reported from humans, birds and mosquitoes in Austria, Belarus, Bulgaria, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Italy, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Ukraine and the UK.

Public health importance: In Finland Sindbis is the causative agent for Pogosta disease, an epidemic rash-arthritis occurring in late summer, with an annual incidence of 2.7/100000. The morbidity is highest in 45- to 65-year-old females and lowest in children. Subclinical SINV infections were 17 times more common than clinical ones. The SINV-antibody prevalence in fertile-age females was 0.6% in 1992; the estimated seroprevalence in Finland is about 2% (Brummer Korvenkontio *et al.*, 2002). The disease may lead to chronic musculoskeletal discomfort and arthritis and is thus of public health importance.

**Ockelbo virus**

Ockelbo disease, caused by a Sindbis-related virus transmitted to man by mosquitoes, was first described in the central part of Sweden in the 1960s (Niklasson & Vene, 1996). Ockelbo virus circulates in a mosquito-bird-mosquito cycle, with *Cs. morsitans* and *Culex pipiens* and/or *Cx. torrentium* as enzootic vectors. The virus has also been isolated from *Aedes cinereus, Ochlerotatus communis* and *Oc. excrucians* in Sweden. The disease, as Ockelbo disease, has been reported only from Sweden.

Public Health Importance: Some 30 cases a year are reported, especially from central Sweden but Lundstrom *et al.* (1991) believe that there are 600 to 1,200 asymptomatic and/or unreported cases a year in the country. Arthralgia is the dominating feature of Ockelbo disease and may immobilize patients for a week and persist for a month, (Niklasson *et al.*, 1988).

**Tahyna virus**

Tahyna virus is a member of the California complex of arboviruses; the virus appears to be present in most countries of Europe. The apparent vectors of this virus are diverse, but are mainly flooded pasture breeding *Aedes* species. Bardos *et al.* (1978) isolated the virus from a pool of *Cs. annulata* larvae in Moravia, in the Czech Republic and Hubalek *et al.* (2000) isolated it from *Ae. vexans* also in Moravia. It has also been isolated from this species in Serbia, and from *Oc. caspius* in Germany (Pilaski & Mackenstein (1985).

Public Health Importance: In human patients the virus may present with influenza-like symptoms. In some cases, meningoencephaltis and atypical pneumonia have been observed, but no cases of death have been reported (Bardos, 1976). Danilov (1990) found Tahyna virus to be very common in the Czech Republic, particularly in children in the areas he surveyed. Every seventh influenza-like case and every fifth case with manifestations of meningoencephalitis can be ascribed to this virus. In Sverdlovsk Province, Russia up to 60% of the population examined carried antibodies for this virus, which appeared to be associated with viral encephalitis (Glinskikh *et al.*, 1994). In view of the prevalence of this virus in most of Europe and its association with disease in several countries, a surveillance of possible clinical cases is warranted.

**Flaviviridae**

The viruses in this group are part of the Japanese encephalitis complex and the mosquito-borne viruses include dengue and Kunjin viruses, Japanese encephalitis, Murray Valley encephalitis, Rocio virus, St. Louis encephalitis and West Nile virus. Of these only West Nile virus is endemic in Europe. In 1927-1928 dengue was the cause of a massive outbreak in Athens, Greece involving some 650,000 residents and over 1,000 deaths. The vector of this virus is *Ae. aegypti* and with its disappearance from southern Europe dengue transmission ceased. However, the introduction and subsequent spread of another member of the subgenus *Stegomyia* and occasional vector of dengue, *Ae. albopictus*, into Europe, may put some areas of Europe at risk to renewed transmission of dengue (Rodhain, 1995).

**West Nile virus**

First described in Uganda in 1937, it is present in much of Africa, Asia and Europe and has recently spread to North America. It is transmitted to man mainly by culicine mosquitoes and is a human, equine, and avian neuropathogen. It is widely endemic in Europe and the virus is maintained in nature in a mosquito-bird-mosquito transmission cycle. The most important vector, especially in eastern Europe is *Cx. pipiens* but the virus has been isolated from many other species. In outbreaks in the south of France in 1962-1965, *Cx. modestus* was apparently the prime vector though the virus has also been isolated from *Oc. cantans* in France, from *Coquillettidia richiardii* and *Oc. caspius* in Bulgaria, from *Ae. cinereus* and *Ae. vexans* in the Czech Republic, and from *Anopheles maculipennis* in Portugal and Ukraine. Hubalek & Halouzka (1999) in their comprehensive review of West Nile virus in Europe provide a list of all the species from which the virus has been isolated. There is serological evidence of WNV in both resident and migrant bird populations in the UK (Buckley *et al.*, 2003) but there have been no isolations of the virus from birds or mammals, nor have there been any human cases in the UK.

Public Health Importance: Infection with West Nile virus can be asymptomatic or cause an influenza-like illness. Severe manifestations include meningitis and meningoencephalitis, particularly in the elderly. The fatality/case ratio and disease incidence increases with age. The case fatality rate in the large outbreak in Romania in 1996, was 15.1% in patients with acute encephalitis, 1.8% in those with acute meningitis and 0% in the acute febrile disease. In the 1996-1997 outbreak, 767 clinical cases of WNV were reported with 17 deaths, i.e. a case fatality rate of just over 2%. However, it is estimated that about 70,000 (range 43,000-96,000) residents had probably been infected during the epidemic, 0.5% of whom developed encephalitis (Hubalek, 2001, unpublished report). The virus has been isolated from humans, animals, birds or mosquitoes in Albania, Austria, Belarus, Bosnia, Bulgaria, Croatia, Czech Republic, France, Greece, Hungary, Italy, Moldavia, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain and Ukraine (Hubalek & Halouzka, 1999). In 2003 two human cases and three equine cases of WNV were reported from the Var region of southern France (unpublished report). From tropical Africa, WNV is transported annually to temperate climates to the north in Europe and to the south in South Africa. Reports of clinical disease due to natural WN virus infection in wild or domestic animals are much less common than reports of infection (virus isolation or antibody detection).

Until recently, records of morbidity and mortality in wild birds were confined to a small number of cases and infections causing encephalitis, sometimes fatal, in horses were infrequently reported. In the period 1996-2001, there was an increase in outbreaks of illness due to WN virus in animals as well as humans. Within the traditional range of WN virus, encephalitis was reported in horses in Italy in 1998 (Autorino *et al.*, 2002), and in France in 2000 (McLean *et al.*, 2002). In view of the endemicity of the virus in many parts of Europe, the availability of competent vectors, and the constant introduction in migrating birds, it is likely that outbreaks will continue to occur and that the infection will spread. Outbreaks of the diseases may occur after long periods of silence and continued surveillance of WNV is essential.

**Malaria**

At one time malaria transmission occurred across much of Europe, limited only by the 15°C July isotherm, and included Denmark, Finland, Sweden and large parts of northern Russia (Hackett 1937). The disease was a major health problem in northern and western Europe. It was particularly severe in the countries bordering the Mediterranean and in inland parts of eastern Europe, where a combination of virulent parasites, efficient vectors, suitable breeding sites and favourable climatic factors contributed to a high prevalence and significant mortality (Kuhn *et al.*, 2003). *Plasmodium vivax* was almost the sole species of parasite outside of the Mediterranean basin.

Following a peak at the beginning of the 20$^{th}$ century, malaria transmission began to decline as a result of ecological changes, especially in agricultural practices, and in the elimination of many of the larval habitats of *Anopheles* vectors by the drainage of swamps and marshes. Improvements in the availability of medical services, eventually followed by active control campaigns following the second World War, interrupted transmission and led to the eradication of the diseases by 1975.

The primary vectors of malaria in Europe were members of the *Anopheles maculipennis* complex. Eighteen species were considered as malaria vectors (Snow, 1999). Among these, most important vector species were *An. sacharovi* in Greece, *An. labranchiae, An. sacharovi* and *An. superpictus* in Italy and the south of France, *An. atroparvus* in the Netherlands, *An. messeae* in Poland and Russia, *An. atroparvus* in the UK, and *An. atroparvus* and *An. sacharovi* in the area of the former of Yugoslavia. The distribution of the European *Anopheles* species has been reviewed by Ramsdale & Snow (2000) and for European Russia by Sokolova & Snow (2000). *Anopheles* population densities remain high or even show an increasing trend in many areas of Europe; as an example *An. labranchiae* was almost eradicated from Italy 50 years ago, the species is now common in rice fields in several regions (Romi, *et al.*, 1997). In the region of Moscow, Russia, densities of *An. messeae* had been greatly reduced by the DDT control operations that continued until 1959. However by 1977 densities had returned to those of the 1940s (Sokolova & Volegova, 1980), and were high enough to constitute a risk of the reintroduction of malaria transmission, which indeed, has begun to occur (Makhnev, 2002).

Public Health Importance: Due to the large numbers of imported cases of malaria reported every year, malaria remains a public health problem in Europe 30 years after its eradication. The greatest problem is the frequency with which malaria is imported into Europe by tourists, migrants and business travellers coming from endemic

areas. The European Office of the World Health Organization has reported that from 14,000 to more than 15,000 cases of malaria were imported into Europe in 1998-2000. The greatest numbers of imported cases were about 8,056 cases into France in 2000, followed by 2,069 into the United Kingdom, 986 into Italy and 732 into Germany. It must be considered that the numbers of cases are underestimated, as many cases are not correctly diagnosed.

The vast majority of the 32,394 autochthonous cases reported in the year 2000 occurred in the countries of the Caucasus region of Eastern Europe. Including both imported and autochthonous cases the total number of reported malaria cases in the WHO European Region in 2000 was 47,925. While most of the cases of malaria being transmitted in the Caucasian region are due to *P. vivax*, most of the cases imported into Western Europe are due to *P. falciparum*, most of which is imported from West Africa. In a large percentage of the cases of introduced malaria, the patients had not complied with the recommendations for chemoprophylaxis or were unaware of them. There have been treatment failures but these are usually the result of poor compliance with the recommended regimes for chemoprophylaxis rather than resistance to the drugs (Ralaimazava *et al.*, 2003). Within the decade 1989-1999, 680 people died from imported cases of *P. falciparum* infection in the WHO European Region.

There have been an increasing number of autochthonous cases of malaria in Western Europe; most are due to transmission by local *Anopheles* populations of malaria infections imported by migrants, infected tourists or business travellers returning from visits to malaria endemic countries. Two cases of *P. vivax* were probably due to *An. labranchiae* transmission of the infection from local residents returning from a family visit to India (Baldari *et al.*, 1998). Two children, who had never been abroad, were infected with malaria in a hospital in Duisburg, Germany, where a child with chronic malaria has been hospitalized at the same time. There was evidence that the vector was *An. plumbeus*, which had been found in the vicinity of the hospital, (Kruger *et al.*, 2001). Eighteen cases of *P. vivax* occurred in Bulgaria, on the border with Macedonia and Greece. The origin of the outbreak was thought to be a migrant worker who had passed through the area on his way to Greece (Vutchev, 2001). Autochthonous cases of *P. falciparum* were diagnosed in Evros Province, northern Greece in 1994-1995. None of the infected individuals had travelled to malaria endemic areas (Kampen *et al.*, 2002). There have been about 85 reported cases of "airport malaria" in Belgium, Germany, France, Italy, Netherlands, Switzerland and the UK due to the inadvertent transport of live, infective mosquitoes aboard aircraft arriving from tropical countries where vector-borne diseases are endemic. There is a need for the disinfection of aircraft coming from airports in tropical disease endemic areas into non-endemic areas (Gratz *et al.*, 2000).

The occurrence of autochthonous cases demonstrates that where suitable vectors are present in high enough densities local transmission can take place. While small outbreaks may occur in Western Europe, the status of the public health systems, the active surveillance of communicable diseases, efficient diagnostic services and availability of effective control measures make the renewal of malaria transmission in western Europe other than on a minor scale seems unlikely. On the other hand, Europe has experienced significant warming in recent decades, and this is likely to continue. Climate warming and changes in rainfall patterns may have significant and wide ranging impacts on health, and there is evidence of climatic effect on vector breeding sites as shown by an increase in areas endemic for malaria in Europe (Kovats *et al.*, 1999).

**Dirofilariasis**

*Dirofilaria immitis* and *Dirofilaria (Nochtiella) repens*, have a worldwide distribution and are inadvertent human pathogens. The usual hosts of these infective nematodes are domestic and wild carnivores, particularly dogs though cats have also been found infected. *Oc. caspius* and *Ae. vexans* appear to be the most important vectors in Italy. Increasing travel favours the emergence of zoonotic parasites not usually seen in human hosts. Outside known enzootic areas, diagnosis is often delayed until pathological examination. In France, the incidence of human dirofilariasis has steadily increased and must be considered in the clinical diagnosis of cutaneous or intraorbital nodules, (Cordonnier *et al.*, 2002). In dogs the presence of these endoparasites causes the condition known as canine heartworm.

Public Health Importance: The most commonly reported manifestation of human dirofilariasis worldwide is subcutaneous nodular disease caused by *D. repens*, with over 400 cases reported in the medical literature.

*Dirofilaria repens* is an Old World parasite and has not been described as endemic in the Americas, Japan, or Australia. Endemic foci for *D. repens* exist in southern and Eastern Europe, Asia Minor, Central Asia, and Sri Lanka. Italy is the European country with the highest prevalence of human dirofilariasis (66%), followed by southern France and Corsica, (22%), Greece (8%), and Spain (4%). Cases of canine and human disease have been described in northern European countries, although they have been traced back to exposure during a visit to southern Europe. Due to the prevalence of the causal agent, *D. repens*, in dogs and the many species of mosquitoes that can transmit the infection to man, it is possible that human cases are more common than reported, many cases passing undiagnosed or simply not published (Pampiglione *et al.*, 1996). There has been an increase in the number of cases of dirofilariasis in Italy (Pampiglione *et al.*, 2001) and the extent of infestations in France is probably underestimated (Raccurt, 1999). It is possible that both *D. repens* and *D. immitis* have spread to the south of Switzerland. The mean average temperature would permit development of the parasites in the local mosquito populations, and several dogs have been found positive including one dog which could have had acquired the infection in the canton Tessin, (Bucklar *et al.*, 1998).

**Tularemia**

The bacterial causative agent of tularemia is *Francisella tularensis*; *F tularensis* is found worldwide in more than 100 species of wild animals, birds and insects. It produces an acute febrile illness in humans. There are two types; type A, occurs mainly in North America and is more virulent than *F. tularensis* subsp. *holarctica*, or type B, which occurs throughout the Northern Hemisphere. Type A is usually transmitted to humans by tick bites or contact with rabbits; type B is associated with water and animals living near water, and its transmission is more complex. The route of transmission and factors relating to the host and the organism influences the presentation. Where transmission is by vectors in Europe they are generally ticks. However, there are reports from Sweden and elsewhere which have also implicated mosquitoes. In Sweden most cases occur within a relatively small area in the central part of the country, with only sporadic cases in other areas. In recent years, however, the disease seems to have spread to areas south of the disease-endemic area. This shift was apparent in the 2000 outbreak, when 187 (40%) of 464 cases were reported to have been transmitted south of the disease-endemic area. The reason for this spread is unknown. Most cases occur in the late summer or early autumn and are thought to be transmitted by mosquitoes, (Tarnvik *et al,* 1996). A multivariate analysis of the 2000 outbreak in Sweden concluded that risk was associated with mosquito bites or ownership of a cat, but that mosquito bites were more important (Eliasson *et al.*, 2002). By contrast, Hubalek & Halouzka (1997) collected large numbers of *Aedes* species and ticks in a tularemia endemic area of the Czech Republic; none of the 9,167 mosquitoes carried *F. tularensis* while 30 isolates were recovered from *Dermacentor reticulatus* ticks. The authors concluded that mosquitoes are not vectors of the infection in the Czech Republic.

Public health importance: Untreated, tularemia has a mortality rate of 5-15%; this rate is even higher with the typhoidal form. Appropriate antibiotics lower this rate to about 1%. The incidence in Europe is unknown other than the reports from Sweden.

**Discussion**

The relative importance of the various mosquito-borne diseases in Europe has changed considerably since the beginning of the 20$^{th}$ century. Malaria, one of the most serious public health problems on the continent, was eradicated by 1975. However, sporadic autochthonous cases still appear in Western Europe, as a result of transmission of the parasite from infected migrants or tourists and, occasionally, from infected *Anopheles* imported aboard aircraft, or in baggage, or even ships, arriving from endemic areas. In Eastern Europe a serious resurgence of malaria has taken place in the countries of the Caucasus and local transmission has occurred as far north as Moscow. While the public health burden of malaria has been greatly reduced, the constant importation of active cases gives rise to autochthonous transmission and the active surveillance of malaria and the control of its vectors must continue.

Mosquito-borne arboviral diseases have certainly always existed in Europe when global temperatures permitted their transmission, but their identity, distribution and incidence only became known when suitable laboratory diagnostic methods were developed. Vector and potential mosquito vector populations exist in high densities in virtually every country; indeed, ecological changes have resulted in increases of population densities and spread

of their distribution. Climate change has resulted in changes in the migration patterns of reservoir birds and greater mosquito-bird contact. Serious outbreaks of West Nile Virus with some mortality have recently occurred in several countries in Europe. The persistence of the virus and its potential for rapid spread as seen in North America from the time of its invasion in 1999 to the present, emphasize the necessity for continuing surveillance and control of the vectors. New mosquito-borne viruses continue to emerge in Europe. The appearance in Austria in 2001 of African arbovirus, Usutu virus, has had a serious effect on the avian populations in that country, though its potential for disease in man and animals is unknown (Weissenbock *et al.*, 2002). There is now serological evidence that this virus, never before detected outside of Africa, is present both in resident and migratory birds in the UK (Buckley *et al.*, 2003).

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