

ECDC THREAT ASSESSMENT

Outbreak of West Nile virus infection in Greece, July–August 2010

Update as of 26 August 2010, following the preliminary findings
of the ECDC expert team in the field

Source and date of request

Internal decision, following EWRS message from Greece, dated 7 August 2010

Public health issue

- Newly identified risk area of West Nile virus transmission in Europe
- Blood safety concerns

Consulted experts

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Disease background information

West Nile virus (WNV) is transmitted by mosquitoes (mainly of the genus *Culex*) with wild birds as its natural amplifying hosts. Birds also play a role in the geographic dispersion of WNV. Human cases have been reported from Romania since the 1960s, and sporadic outbreaks have occurred in several countries in eastern and southern Europe in the past 15 years [1]. The presence of the virus in birds suggests ongoing transmission and probable endemicity of WNV in Europe. Humans are mainly infected through mosquito bites, few infections through organ transplantation and blood transfusion have been documented in North America [2-4].

After the infectious bite, an incubation period of 2–14 days precedes symptoms which range from mild fever and malaise, moderately severe disease (high fever, red eyes, headache and muscle ache) to meningitis or encephalitis. The most severe manifestations are in the elderly and the debilitated [5]. However, 80% of the infected persons remain asymptomatic. No specific treatment or vaccines are currently available. Preventive measures include informing the at-risk population about how to reduce exposure to mosquito bites and ensure the exclusion of blood donations from donors living in and visiting affected areas, if feasible.

Phylogenetically, WN viruses are assigned to at least two main lineages. Lineage 1 has been identified in the majority of outbreaks in Europe and the Americas in humans and horses. Lineage 2, in contrast, was identified outside of Africa only recently: in 2004 and 2005 in goshawks in Hungary; in 2007 in Volgograd, Russia; and in 2008 in wild hawks and a captive kea in Austria [6, 7].

Following the large urban outbreak in Bucharest (Romania) in 1996–1997 [8], transmission of WN viruses to human and/or horses has been documented on several occasions:

- in the Czech Republic (1997) [9];
- in France (2000, 2003, 2004, 2006) [10-12];

- in Italy (1998, 2008-2009) [13-17];
- in Hungary (2000-2008) [18];
- in Romania (1997-2001, 2008-2009) [19, 20];
- in Spain (2004) [21-23]; and
- in Portugal (2004) [24].

More recently, in 2009, human cases of WNV infection were reported from Hungary (7 cases), Romania (2 cases) and Italy (16 cases). In July 2010, Portugal reported a probable case of WN virus infection, which was the first (probable) case of WN virus infection reported in 2010 in the EU.

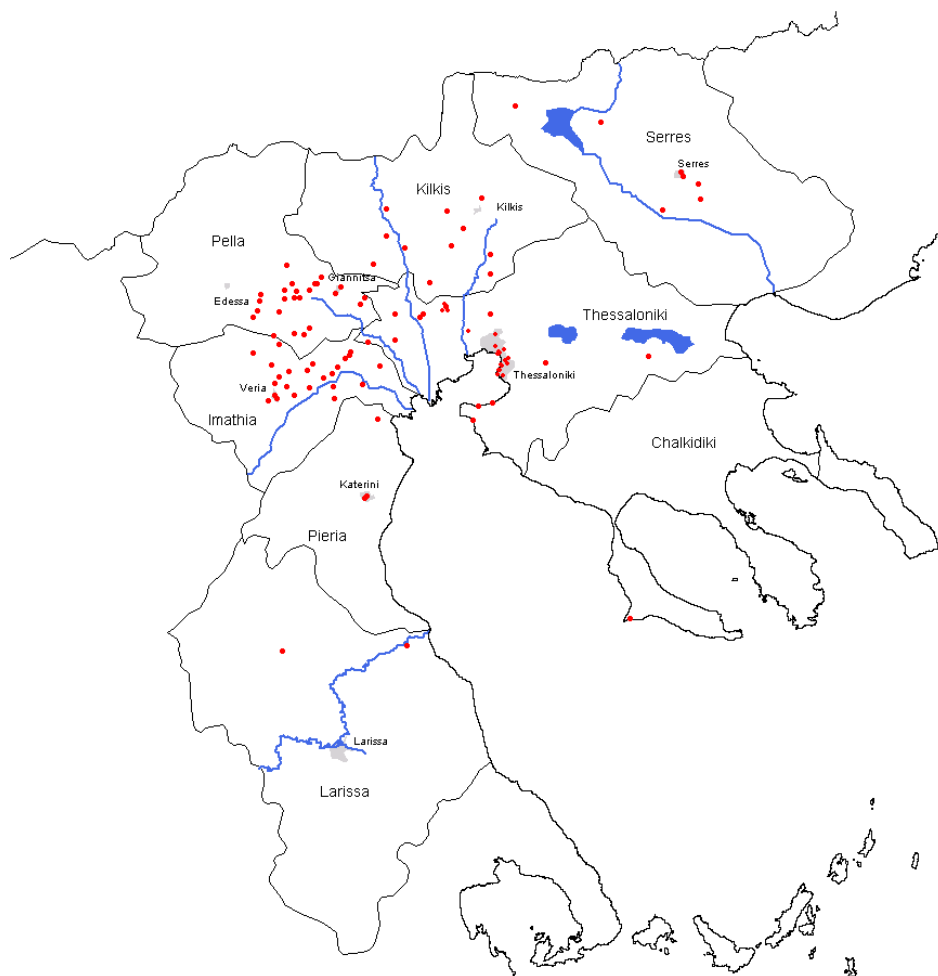
In Greece, serological studies in the 1970s detected WNV antibodies in animals (horses, cattle, goats and rabbits) and humans [25]. Surveys conducted in the 1980s and in 2007 identified WNV antibodies in approximately 1% of selected populations in the region of Central Macedonia. Serum samples collected from 392 residents from northern Greece (Imathia) in 2007 revealed six positive samples for WNV, four of which (1%) were confirmed by micro-neutralisation assay [26, 27]. In contrast, a survey of 9590 blood donations and 115 CSF samples from patients with aseptic meningitis in Greece in June to October 2006 and 2007 revealed no positive results for WNV by NAT (Nucleic Acid Amplification Testing) [28].

Event background information

The current outbreak was reported by the Greek authorities on August 7, 2010. As of 26 August, 2010, a total number of 130 laboratory confirmed cases of WNV infection have been reported at the national level in Greece; of these 108 (83%) presented with neuro-invasive symptoms and 9 deaths have been reported [29].

According to a recent comprehensive epidemiological update of 81 case reports up to 22 August, 2010, the median age was 70 years (71% over 50 years); 56% were male [30]. The current geographical distribution of cases shows that the majority of cases (71.6%) live in the lowland of the region of Central Macedonia. Two cases were reported from a district south of Central Macedonia.

Figure 1: WNV neuro-invasive cases reported in Greece, 26 August 2010 (n=108)



The lowlands from which the majority of cases are reported are located between three major rivers (Axios, Loudias and Aliakmon). This area is primarily used for agriculture production and rice paddies. The three rivers converge into a common delta, which is a well-known resting ground for migratory birds. Mosquito vectors of WNV, including *Cx. modestus* and *Cx. pipiens* are known to be present throughout Central Macedonia.

Following entomological surveillance activities in the affected region (August 16, 2010), preliminary lab analysis suggested the presence of WNV of lineage 2 in a pool of *Culex* mosquitoes [31]. No virus has been isolated recently from human cases. Also, an initiative by the Veterinary Department of the University of Thessaloniki has provided evidence of recent clinical infection with WNV in horses near to the city of Thessaloniki; five cases of equine encephalitis were reported to the European ADNS System on 27 August.

Greek authorities have implemented a series of public health measures, including:

- Human surveillance: a nationwide passive surveillance system for WNV infection and active surveillance system in the affected areas.
- Vector control: adult mosquito control with ultra-low-volume (ULV) spraying is implemented in villages with neuroinvasive cases.
- Public communication: information about the outbreak, transmission, symptoms and personal protection measures to prevent mosquito bites is communicated to the public.
- Blood safety: initially, all blood donations from the affected areas were deferred, blood donations were quarantined until testing with NAT for WNV could be performed, and there was a 28-day deferral to donate blood for persons having visited the affected area for one day or more. Now NAT screening capacity has been established in the affected areas of Central Macedonia.
- In terms of animal surveillance, there is a passive surveillance for encephalitis in equines all over Greece, but there is no sentinel monitoring system for the circulation of WNV in birds or equines.

ECDC threat assessment for the EU

After the recorded outbreak of WNV infection in humans in Bucharest, Romania, in 1996–1997 with 500 cases reported, this is the second largest outbreak of the disease in the EU [32]. Even though the identification of the implicated virus or viruses infecting humans is pending, evidence of circulation of lineage 2 virus in the mosquito population would increase the number of EU countries where this lineage has now been identified. It has been suggested that lineage 2 virus is not associated with equal pathogenesis of disease as lineage 1 WNV. However, the clinical picture of the current outbreak – just as the lineage 2 outbreaks in Russia (2007) and South Africa (2007–2008) – suggests that both lineages are capable of producing severe disease [33].

Whether this outbreak is due to climatic factors favouring unprecedented mosquito reproduction, an increased virulence in strains of WNV circulating in northern Greece (though unlikely) or some other factor, or a combination of them not accounted for, remains to be elucidated. WNV circulation and transmission is hugely complex, and defined reasons for outbreak occurrence in humans might never be understood fully. Comparison of climatic conditions in other European countries where transmission has been documented would be interesting.

The epidemiology of the outbreak in northern Greece is consistent with what is known about WNV infection. The majority of neuroinvasive cases are in elderly, with a case fatality ratio of about 10% among severe cases. The number of neuroinvasive disease represents only a small proportion of the total number of persons infected in the affected areas. In terms of geographic distribution, with the presence of birds (migrating and resident) and bridge vectors, the region of Central Macedonia presents all the ecological components for successful transmission of WNV to humans. A clear epicentre of the outbreak is in the lowland plains between and around the Aliakmonas and Axios rivers, from where the majority of cases are reported. The human cases currently reported from the city of Thessaloniki, however, suggest that there might be an established urban cycle of transmission. For the remainder of the cases residing outside of the outbreak's epicentre, it is possible that several have acquired their infection by spending time in the epicentre of the outbreak. For others, such exposure is less clear following case investigations, and therefore transmission of virus to humans in these areas cannot be excluded from these areas.

Publicly available information regarding viral circulation in horse and bird populations in Central Macedonia is limited at the present time. However, serological studies indicate that WNV has been circulating in these animal populations and humans in the region for several years [26, 27]. The identification of lineage 2 virus in a *Culex* mosquito pool caught in a village from where a confirmed human case was reported in August 2010, as well as the ongoing reporting of human WNV infections in this region strongly indicate that viral circulation and its transmission to humans is currently well established.

Public health measures to control the outbreak have been implemented in the entire region of Central Macedonia as well as in the district of Larissa in the neighbouring region. Enhanced surveillance for neuroinvasive disease is ongoing (passively nationwide, and actively in affected areas). However, the outbreak may well continue (including newly identified villages) until the mosquito season ends. While unlikely, a further extension of the outbreak

outside of the region of Central Macedonia cannot be excluded; close surveillance of the surrounding areas will assure rapid identification of newly affected areas.

With regard to blood safety, a general deferral policy on all blood donations from the affected areas would negatively impact the national availability of blood. For this reason, NAT screening has recently been implemented on all blood donations in the affected areas, and it is likely that any contaminated blood unit from asymptomatic donors will be identified. Furthermore, the 28-day deferral policy implemented for the remainder of the country for visitors to the affected areas is likely to avoid any significant contamination of national blood supplies.

The precise reasons for the existence of the current outbreak of WNV infection in humans in the region remain unclear. However, meteorological data from 2010 for Central Macedonia suggest that there has been an unusual rainfall pattern and that temperatures were unusually high in July and August [26]. Such climatic factors are believed to have increased the abundance of mosquitoes and shortened the transmission cycle in the vectors, leading to increased human cases.

Considering the current epidemiological situation of WN in Central Macedonia, as well as the particular climatic factors and their influence on the local mosquito populations, this outbreak is considered to be of limited risk for spread to other EU Member States. However, ecological parameters in the region are currently favourable for viral activity. This is evidenced in recent reports of a large outbreak in humans ongoing in Russia, a single probable human case from Portugal and outbreaks of WN in horses from Morocco. Therefore, countries with some evidence of previous WNV circulation as well as their neighbouring countries would benefit from strengthened surveillance to ensure the early detection of possible transmission of this virus to humans. Personal protection from mosquito bites is advisable to any person resident or visiting these areas.

With regard to blood safety, the EU Commission Directive 2004/33/EC, Annex III.2.2.1, states that blood banks should defer blood donation from any blood donor for 28 days following their return from an affected area with ongoing transmission of WNV to humans. In Greece, these areas are currently identified as Central Macedonia and the district of Larissa, which corresponds to the current epidemiology of the outbreak. Surveillance for human neuroinvasive disease in Greece appears to be sufficiently sensitive to identify newly affected areas in a timely manner, which can then serve to inform blood safety experts in other EU Member States.

Conclusions

The current outbreak in Greece is the first large outbreak of WNV in humans in Europe since the Romanian outbreak in 1996–1997. The presence of West Nile virus is well-documented in several European countries. Climatic conditions (temperature and humidity) favour the presence and the multiplication of *Culex spp.* from May to October in the affected zones. At the same time, there has been an increase in the number of cases in the EU over the past decade. The possibility that this reflects a changing epidemiology needs to be considered seriously [34, 35].

The current outbreak in northern Greece is limited to clearly identified administrative areas and is expected to continue for the duration of the mosquito season in 2010.

For the remainder of the EU, the risk to EU citizens is limited. However, vigilance in the human and veterinary sectors in countries with ecological parameters favourable for viral transmission (and evidence of viral circulation) is warranted.

This threat assessment will be updated as needed, depending upon the availability of new relevant information.

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