ECDC Threat Assessment

Review of epidemiological situation on West Nile Virus infection in the European Union

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PUBLIC HEALTH ISSUE
West Nile Virus infection in humans reported from several European Member States

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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 hosts. Birds also play a role in the geographic dispersion of WNV. While human cases have been reported from Romania since the 1960's, sporadic outbreaks have occurred in several countries in eastern and southern Europe in the past 15 years[1]. The presence of the virus in amplifying hosts (birds) suggests ongoing transmission and probable endemicity of WNV in Europe.

While 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 reported mainly in the elderly and the debilitated[5]. However, 80% of the infected persons remain asymptomatic. No specific treatment or vaccines are

currently available. The main preventive measures if feasible are aimed at informing the at-risk human population, reducing exposure to mosquito bites and exclusion of blood donations from donors living in and visiting affected areas.

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

In Europe following the large urban outbreak in Bucharest (Romania) [8], several instances of WN virus transmission have been identified in humans and/or horses

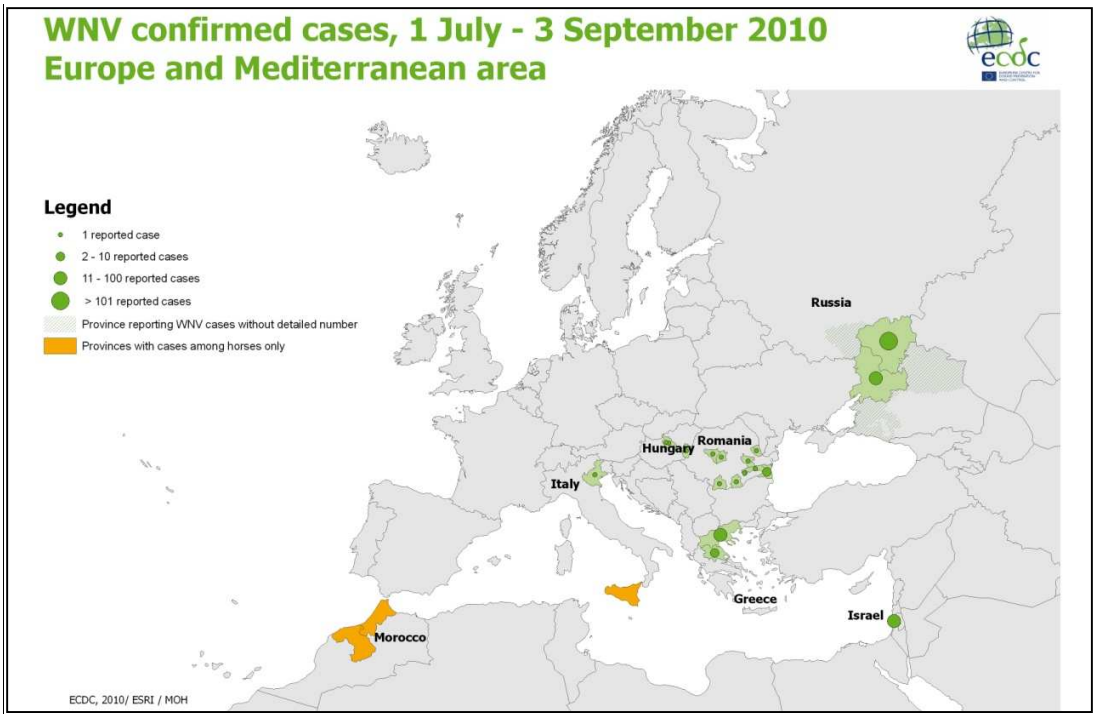
- in the Czech Republic (1997) [9]
- in France (2000, 2003, 2004, 2006) [10-12]
- in Italy (1998, 2008-2009) [13-17]
- in Hungary (2000-2008) [18]
- in Romania (1997-2001, 2008-2009) [19, 20]
- in Spain (2004) [21, 22]
- and in Portugal (2004) [23]

More recently, in 2009, human cases of WNV infection were reported from Hungary (7 cases), Romania (2 cases) and Italy (16 cases).

EVENT BACKGROUND INFORMATION

To date in 2010, four EU Member States have reported probable or confirmed cases of WNV infection in humans. The following information summarises the available information on these events. The map illustrates where the current reported cases from WNV infection in the EU have been reported as well as known outbreaks reported through the media or official sources in Russia, Israel and Morocco (in horses).

Map



NB: areas in green indicate from where confirmed WNV infection human cases are reported. Areas in orange are areas from where WNV infection is confirmed in horses.

1. Portugal [24]

A single probable case of WNV infection was reported by Portugal on 27 July in a 55 year old woman living in the region of Lisboa e Vale do Tejo in a rural area near the Sado river estuary. Her symptom onset (high fever, rash, cervical adenopathies, but no neurological signs) was around 5 July. Information provided by the clinician indicated that she had been bitten by mosquitoes prior to getting sick. WNV specific titres for IgM and IgG between two paired samples suggested a recent infection with WNV, but confirmatory tests by neutralisation conducted in RKI, Germany were negative.

Following the detection of this case, the following public health measures were implemented by the Portuguese authorities:

1. Human surveillance: active surveillance for suspected human cases near residence of probable case, active review of hospital records and increasing awareness of clinicians;
2. Veterinary surveillance: serological studies in horses and birds of the area; necessary structures for detection of clinical cases in horses were reinforced;
3. Entomological surveillance: recent data from the affected area demonstrated no infected mosquitoes with WNV infection around the area of residence of the case;
4. Blood safety: the EU rapid alert system was activated and necessary measures taken at the national level.

In Portugal, despite these intensive efforts, the single probable case has not been confirmed and no further evidence of possible WNV circulation in the Lisboa e Vale do

Tejo region of the country has been identified. Previously WNV circulation has only been detected in the Algarve region, with associated human cases in 2004 [23, 25, 26].

An ECDC Threat Assessment for this event was issued on August 2, 2010.

2. Greece [27-29]

Between 7 August and 3 September, 2010, the Greek authorities have reported 173 laboratory confirmed cases of WNV. The first cluster of neuro-invasive disease was detected at the Hospital for Infectious Diseases of Thessaloniki on the 4th of August 2010, samples were tested on the 5th of August and the official notification of confirmed human cases of WN infection was made on the 7th of August. Five horses with confirmed WNV infection, tested at the Laboratory of Microbiology and Infectious Diseases, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, were reported to the Animal Disease Notification System (ADNS) on 27 August. All five were from Central Macedonia.

From the most recent weekly comprehensive epidemiological update posted by the Greek health authorities on September 3, 2010, the situation is the following:

- 173 laboratory confirmed cases of WN infection were reported at the national level in Greece; of these, 148 (86%) presented with clinical manifestations that is consistent with neuro-invasive disease. A total of 15 deaths were reported in persons over 70 years of age. Of the 173 cases, 39 continue hospitalised and nine are in the intensive care unit.
- For 142 of 148 neuro-invasive cases for which the information was available:
    - 61% are in persons over 70 years of age;
    - 11% of reported neuro-invasive cases are in persons under 50 years of age;
    - 56% of these cases are males.

According to the most recent epidemic curve, the first reported case had disease onset on the 6 July and the last on 26 August for persons whose laboratory diagnosis was conducted before 1 September.

The geographic extension of reported human cases is currently restricted to the region of Central Macedonia and the district of Larissa, which is located to the south of Central Macedonia. Most of the patients are residents or have activities of the lowlands in the larger area of the delta of rivers Aliakmonas and Axios Of the 142 neuro-invasive cases for whom this information was available, highest incidence is noted in the district of Imathia (23.6/100,000 population), followed by Kilkis (22.7), Pella (12.7), Pieria and the city of Thessaloniki.

Since the detection of the outbreak, the implemented public health measures include:

1. Human surveillance: a nationwide system for passive surveillance of neuro-invasive cases of WN infection is in place. Additionally active surveillance is being conducted in the hospitals in the prefectures with confirmed human cases.
2. Veterinary surveillance: there is passive surveillance for encephalitis in equines all over Greece. In August 2010, a sentinel surveillance system for horses and wild

birds has been initiated by the Directorate General of Veterinary Services from the Animal Health Directorate in the Ministry of Rural Development and Food.

3. Entomological surveillance: no government system for entomological surveillance is in place. However, mosquito monitoring is undertaken by vector control contractors. Vector control activities (including ultra-low-volume spraying) to tackle adult mosquito populations are conducted in villages where neuro-invasive WNV infection cases are detected.
4. Blood safety: initially, all blood donations from the affected areas were deferred, blood already collected was quarantined for Nucleotide Acid Amplification Testing (NAT), and there was a 28-day deferral for persons having visited the affected area for one day or more. Currently, blood donations from districts where human WNV infection cases are notified are being deferred. For other districts in Central Macedonia, NAT is being done on donations.
5. Public communication: widespread media coverage and formal communication/public education campaigns addressing the outbreak, transmission, symptoms and personal protection measures to prevent mosquito bites have been implemented

This is the first human outbreak of WNV infection reported from this country despite previous evidence from serological studies that the virus has been circulating in northern Greece [30-32]. Furthermore, a *Culex* spp. mosquito pool was found positive for lineage 2 WNV in a village where a confirmed case was identified which has not been commonly identified in humans or horses in the EU[33]. In comparison to other EU countries, the WNV transmission season occurred earlier in Greece with human cases reporting disease onset in the beginning of July.

An ECDC threat assessment was issued on 13/08/2010 and an update following an ECDC mission on 27/08/2010.

3. Italy

A single case of WN fever (non-neuro-invasive disease) has been reported in the region of Veneto during August 2010. This case was detected as a result of the enhanced surveillance system for summer fever implemented in the region Veneto.

No specific measures have been implemented following the identification of this case of WN fever. However, there are ongoing surveillance systems for the monitoring of the WNV situation. These include:

1. Human surveillance: a nationwide passive surveillance system for neuro-invasive cases is in place. Upon confirmation of WNV infection in humans, each region is in a position to implement active surveillance cases for further human cases. In Veneto specifically there exists an enhanced surveillance system for ‘summer fevers’.
2. Veterinary surveillance: routine surveillance for equine illness is well established nationwide. According to the ADNS three horses with encephalomyelitis from WNV infection were reported from Trapani, Sicily in 2010.
3. Entomological surveillance: recent testing of pools of mosquitoes in Veneto (which are under routine surveillance) has resulted in the identification of PCR positive pools of mosquitoes for WNV.

4. Blood safety: for the current case no additional blood safety measures are in place. NAT screening capacity is in place in blood centres in Veneto and Emilia Romagna.

In Italy, where human cases of WNV infection with neuro-invasive disease were reported in 2008 and 2009 from the regions of Emilia Romagna and Veneto [34, 35], the single reported case of WN fever in 2010 is evidence that WNV is maintained in this region of Italy. The reported equine WNV infections from Sicily, suggest that WNV transmission also occurs elsewhere in the country.

4. Romania [36]

Starting on August 30, 2010, the Romanian authorities reported through EWRS the existence of seven confirmed and three probable human cases of WNV infection. On 3 September 2010, there are 15 confirmed and probable cases reported.

Epidemiological information available for the cases includes:

- Dates of onset vary between end of July and throughout August. There are cases with dates of onset after 15 August, 2010;
- There are 11 males and four females;
- Age distribution: median age of 50 years (range 18-79)
- Two persons have died (both over 75 years of age) and a third is in critical condition;
- The geographic distribution of the current cases is: 4 confirmed cases in district Constanta, 1 confirmed case in each district of: Alba, Bucharest, Buzau, Dolj, Galati, Ialomita, Sibiu and Teleorman and 1 probable case in each districts of: Cluj and Mures;
- There is a cluster of human cases in 3 districts from central Transylvania where few cases have been reported from in the past.

The current implemented public health measures include:

1. Human surveillance: enhanced surveillance is in place nationwide for neuro-invasive cases and retrospective laboratory testing for cases with meningitis and encephalitis is being conducted.
2. Veterinary surveillance: there is currently no information available from the veterinary surveillance system
3. Entomological surveillance: local authorities have been ordered by the Ministry of Interior to implement vector control activities (upon request of the Ministry of Health)
4. Blood safety: the population from the affected rural areas are being deferred for 28 days for blood donation (from the last date of onset of confirmed cases in those areas). For the neighbourhoods of the major cities from where cases have been reported, deferral policies are only implemented in their neighbourhoods.
5. Public communication: recommendations for prevention of WNV infection have been issued for the public

In Romania in 2008, two cases of neuro-invasive disease from WNV infection were reported from the south of the country (where previous cases had been identified) [37] and two cases of WN fever were diagnosed from central Transylvania, an area previously thought to be free of WNV circulation (personal communication Cornelia

Ceianu). In 2009, a single case of neuro-invasive disease was reported in a person living close to the Danube River [38]. The case reports from 2010 are therefore unusual as they are higher than the previous two years and because the geographic distribution of probable and confirmed neuro-invasive cases extends beyond the normal districts located in the Danube delta. Whether this is a true increase or an artefact of improved surveillance needs to be determined.

5. Hungary [39]

As of September 1, 2010, the National Centre for Epidemiology received a report of three cases of neuro-invasive WNV infection as confirmed by the National Reference Laboratory for Viral Zoonoses.

The patients were 17, 52 and 56 years old females, suffering from meningo-encephalitis. The onset of symptoms was around the middle of August. Two of them are residents of the Central-Hungarian Region, and the third is living in Bekes county.

Currently implemented public health measures include:

1. Human surveillance: enhanced surveillance for neuro-invasive illness is implemented annually, nationwide, between March and October. Epidemiological investigations are launched for each laboratory-positive case for recent WNV infection. Awareness has been raised for clinicians to be on alert for suspected clinical cases of WNV infection and the need for relevant laboratory tests by the National Centre for Epidemiology.
2. The Central Agriculture Office of the Ministry of Agriculture and Rural Development are alerted to closely monitor bird and animal mortality rates in affected counties.
3. Vector control: following flooding around the Danube and the major lakes in Hungary in early summer, the mosquito populations increased dramatically and mosquito control operations have been initiated from June to reduce their abundance.
4. Blood safety: the National Transfusion and Blood Service has been informed about the cases.

In Hungary, between 2003 and 2007 an annual average of 5-6 cases of WNV neuro-invasive infection was diagnosed. In this country, viruses from both lineages 1 and 2 have been reported in birds in 2003-2005 [20]. In 2008 the epidemiological situation slightly changed [18], and 19 cases with neuro-invasive disease were reported from all over the country, whereas in 2009 seven cases were reported [40, 41]. In 2008, lineage 2 WNV was also suspected in human infections.

ECDC THREAT ASSESSMENT FOR THE EU

The outbreak in Greece is the largest human outbreak of WNV infection reported in the EU since 1996. Even though the situation for WNV in Hungary and Italy at the moment is similar to the last two years, the extension of the geographic distribution of reported cases in Romania, the scale of the outbreak ongoing in Greece and the identification of lineage 2 virus in mosquitoes in Greece might all be indicators of something unusual in the epidemiology of this disease.

Unfortunately we still do not have a complete understanding of the factors that influence each of the components of the complex WNV transmission cycle and these remain to be elucidated in the EU-setting, but changing ecological parameters and climate could be a part of them.

It should be noted that case reports from Hungary, Italy and Romania in previous years were in persons that had disease onset between late August and September [14, 17, 18, 20, 34]. It is therefore likely that new cases will be reported from these countries in the weeks to come, as it appears that in these countries transmission to humans of WNV occurs towards the end of the mosquito season. In Greece, as was stated in the previous ECDC threat assessment, the continued increase in cases in humans is expected into October until the end of the mosquito season in the affected areas. Personal protection from mosquito bites is advisable to any person resident or visiting these countries in coming months.

From all EU Member States that are reporting WNV infection in humans this year, the evidence of viral circulation in both birds and particularly horses is not complete. Veterinary surveillance information is needed to establish geographical limits to areas of viral circulation and to assess risk for transmission to humans. This highlights the continued need to strengthen WNV preparedness in the veterinary sectors throughout the EU and to stimulate collaboration between public health and veterinary authorities in all countries from the national to the local level. In Greece and Italy, the identification of WNV in mosquito pools in areas with human cases confirms that active transmission is ongoing here.

Recent reports of WNV outbreaks in horses in Morocco and in humans in Israel, including an imported case in the Netherlands [42], and Russia, suggest that WNV circulation is active throughout Central Europe and the Mediterranean. In this region, there continue to be several gaps in our understanding of the epidemiology of WNV. The strengthening of surveillance systems for humans and horses as well as the strengthening of laboratory capacity to diagnose WNV infection is essential to ensure early detection of transmission in humans as well as to complete the epidemiological picture of WNV.

In terms of blood safety, all countries with reported cases make efforts to apply the EU Blood Directive 2004/33/EC, Annex III.2.2.1 in the lower administrative areas (such as districts and counties) where human cases of WNV infection are being identified. As human surveillance systems are enhanced in all countries currently reporting human cases, it is likely that newly affected areas will be identified early and included in the overall deferral policy of blood donations. However, for other EU MS it would appear opportune to ensure that the blood donation screening questionnaires include questions on travel history in the previous 28 days, with a specific focus on the affected areas that are mentioned in this current threat assessment. It is however also an opportune time for affected countries to make an effort to document the steps employed to assess risk to blood safety with the available epidemiological information, and to record the impact on their national blood supplies following the implementation of the EU Directive. This will assist other countries to strengthen their WNV preparedness and response plans in future transmission seasons.

CONCLUSIONS

WNV circulation is a reality in several countries in the EU, which is confirmed by the reports of human cases and outbreaks in 2010; new areas of transmission are being identified in Greece and Romania. Countries that present areas with favourable ecological parameters for the interaction between infected migratory birds, resident birds, competent mosquito vectors and humans are at risk for the establishment of active and efficient transmission of the virus to humans.

At the EU level, the critical period for WNV transmission is between June and September each year. It is during this time that vigilance in the human and veterinary sectors in countries that have documented historic transmission of WNV or that are at risk for transmission to humans should be strengthened. By ensuring the close collaboration between multi-sectoral surveillance and response systems, effective early warning for the appearance of human cases can be established, which allows for the faster and targeted implementation of an appropriate public health response.

A thorough assessment on the importance of weather patterns, bird migration or other factors in the overall WNV transmission cycle and epidemiology of the disease in Europe would be useful [43].

This threat assessment will be updated as new information becomes available.

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