Risk Assessment Group

CONSULTATIVE SIGNAL ASSESSMENT
PRIMARY RISK ASSESSMENT
EVIDENCE BASED RISK ASSESSMENT
PUBLIC HEALTH EVENT ASSESSMENT

PROBABLE IMPORTED WNV CASE IN HUNGARY COMING FROM BELGIUM

Date of the signal	Date of the PRA	Signal provider	Experts consultation	Method
02/08/2019	06/08/2019	ECDC	**Permanent experts:** Dr Valeska Laisnez (AZG), Dr Romain Mahieu (COCOM-GGC), Dr Paul Pardon (FOD), Dr Carole Schirvel (AViQ), Dr Mireille Thomas (DE), Dr Sophie Quoilin (Sciensano), **Specific experts :** Marjan Van Esbroek (ITM), Dorien Van den Bossche (ITM), Steven Callens (UZGent)	eMail
Date of update	Closing date			

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Signal

On Friday 02/08/2019 we received an email from ECDC enquiring about an imported WNV case, which has a probable place of infection Belgium, diagnosed in 2018 in Hungary and reported in a Eurosurveillance article as follow: "*The case lives in Belgium, started to present clinical signs of acute viral infection 1 day after arriving to Hungary for vacation. Although viral nucleic acid detection was negative, anti-WNV IgG antibody titre was fourfold higher than anti-USUV IgG level; this titre difference was high enough to be indicative of WNV infection. Furthermore, the patient was positive for anti-WNV IgM and IgA. Therefore, in this case an acute WNV infection could be supposed.*"

Description

Event

In 2018, Hungary has diagnosed an imported probable case of WNV, in a 45 years old Hungarian man who lives and works in Belgium (City of Brussels). He travelled to Hungary for vacation on the 22/07/2018, without other travel history nor blood transfusion or organ transplant during the incubation period.
Clinical picture: Disease onset was on 23/07/2018, with the following symptoms: encephalitis, fever, headache and rash. He was admitted to the hospital on 27/07/2018 and was discharged on 30/07/2018. He was diagnosed as West Nile virus neuroinvasive disease (WNND), of which he fully recovered.

Laboratory tests: Only serological tests were done. No viral nucleic acid could be amplified, as neither whole blood, nor urine sample were available for PCR. Results of the serology were as follow:
- 1st serum sample (date of sampling: 30/07/2018) with IFA: Anti-WNV IgG: 1:1280 (positive) and Anti-WNV IgM: 1:10 (weak positive).
- 2nd serum sample (date of sampling: 09/08/2018) with IFA : Anti-WNV IgG: (1:5120) positive and Anti-WNV IgM : 1:40 (positive).

Serological cross reaction was also assessed for Usutu virus and TBEV. Anti-WNV IgG antibody titre was fourfold higher than anti-USUV IgG level. So Usutu infection was discarded (further information on test results Annex 1).
No information on yellow fever and TBEV vaccination was provided.

Interpretation of the results: The results could be explained by a previous flavivirus exposure (possibly WNV), with a secondary infection with another flavivirus in July 2018. Indeed, one would not expect the IgG to be this high 8 days after symptom onset combined with a low IgM titer. In case of a secondary infection, it has been described that the IgM of the actual causing flavivirus can be suppressed and even remain undetectable and that titers of the first flavivirus may react even before the actual flavivirus seroconverts. In Belgium, infection with another flavivirus than WNV seems more likely, such as TEBV or USUTUV, both being present in Belgium (data from animal surveillance and possible human cases of TBE in 2018) and both (possibly) presenting as an encephalitis.

The 2018 West Nile virus (WNV) transmission season was quite unusual, with an early occurrence of a large number of human WNV infections in Europe and EU neighbouring countries. Indeed, a higher number of cases were reported that year compared with transmission seasons in previous years. The total number of reported autochthonous infections (n=2 083) exceeded, by far, the total number from the previous seven years (n=1 832).Compared to the 2017 transmission season, there was a 7.2-fold increase (Annex 2).

In Belgium, only imported cases have been reported so far : two cases in 2018, two cases in 2017 and 2 cases in 2012.
No autochthonous cases have ever been reported.

Cause known?
Yes

West Nile virus (WNV) is a flavivirus related to the dengue, yellow fever and Zika. It is a mosquito-borne disease. The virus is transmitted among birds via the bite of infected mosquitoes (*Culex spp.*) and incidentally humans and other mammals may become infected.

	Most WNV infections in humans are asymptomatic. About 20% of WNV infections in humans may cause West Nile fever (WNF), which is the most common clinical presentation, and is characterised by a sudden onset of symptoms that may include headache, malaise, fever, myalgia, vomiting, rash, fatigue and eye pain. No specific prophylaxis or treatment exist against the disease in humans.
Unexpected/unusual **Unusual**	Having a human case of WNV in Belgium would be unusual but not fully unexpected due to the widespread circulation of the virus in Europe and the presence of the mosquito vector in Belgium. However, so far, all the cases occur in southern, eastern and western Europe (Annex 3) and passive surveillance in wild birds (from 2010 to 2017) never detected virus circulation in Belgium.
Severity **Low**	It is estimated that in less than 1% of cases (approximately one in 150 infected people), patients develop a severe form called West Nile neuroinvasive disease (WNND). This form is characterized by the presence of encephalitis, meningitis, meningoencephalitis, flaccid paralysis with high fever, stiff neck, etc. The lethality rate of severe forms varies from 3% to 15%.
Dissemination (**Low**/~~Medium/High~~)	The probability of having an autochthonous WNV case in Belgium is currently low, but this might change in the future. The risk of dissemination through Substances of human origin (SoHO) is also low if EU blood safety recommendations are properly followed.
Risk of (inter)national spread	There is already spread in Europe as West Nile virus (WNV) infection is endemo-epidemic in Europe. During the transmission season (usually around June - November) the disease affects countries in southern, eastern and western Europe (Annex 3).
Preparedness and response	
Preparedness	In Belgium diagnostic capacities (NRC arboviruses) exist and human passive surveillance of WNV is in place : reporting of probable and confirmed cases by NRC (yearly) and mandatory notification of all cases in Brussels, cases infected in Europe in Flanders and autochthonous cases in Wallonia.
Specific control measures (surveillance, control, communication)	- In humans: passive surveillance of WNV is in place. - In animals: • surveillance for horses does not exist in Belgium. • surveillance of wild birds : surveillance of dead birds was set up in 2010, funded by AFSCA-FAVV. This was carried out by the Royal Belgian Institute of Natural Science and by Sciensano (former CODA-CERVA). The surveillance was stopped in 2017 (no further funding by AFSCA-FAVV). Since then, no birds have been tested. - Substances of human origin (SoHO): standard haemovigilance, biovigilance and post-transfusion/transplantation surveillance exist. Blood banks (Red cross in Belgium) follow recommendations provided in the EU preparedness plan for blood safety. Donors of organs, tissues and cells living in or returning from an affected area are tested for WNV infection. Up to now, Belgium has not been considered as a risk area.
Public health impact	
Public health impact in Belgium (Low/Medium/high)	Currently Low: the probability of having an autochthonous WNV case in Belgium is currently low, but this might change in the future. Having imported WNV human cases is not unexpected.
Recommendations (surveillance, control, communication)	**Regarding the case:** - Request Belgian contact details of this case in order to gather more information (exposure to ticks, check travel information…). - Test sample from patient again and perform further test **Surveillance**: - Considering putting in place passive surveillance for horses (as recommended in the ECDC rapid risk assessment tool for WNV) - Ensure that passive surveillance for wild birds is set up again **Information:** - Increase awareness amongst healthcare professionals (travel clinics and GPs) about WNV in Europe so it will be considered in the differential diagnosis of travelers returning from affected areas : information on the current EU situation can be put in the next monthly newsflash. Information on the risk of acquiring WNF in EU/EEA affected areas should be added in the information page by country of the ITM website, as well as on the website of the Federal public

	service of foreign affairs → RMG : contact ITM and SPF foreign affairs with request to put more information on WNV and WNF on their website.
Actions	→ Sciensano to prepare the information for the next flash and to update the page 'professional' of the website with the current epidemiological situation in Europe → RMG: ensure surveillance in wild birds is re-established. → A blood sample collected in Hungary at the time of disease will be sent to Belgium for further testing by ITM
Decision	From all the information available, we don't think this case has been infected with West Nile virus in Belgium, although we can't exclude it. Despite the low probability of an WNV infection in Belgium, in the context of progressive spread of WNV infections in Europe, a surveillance system of the disease in wild birds need to be set up again.

REFERENCES

1. Nagy Anna, Mezei Eszter, Nagy Orsolya, Bakonyi Tamás, Csonka Nikolett, Kaposi Magdolna, Koroknai Anita, Szomor Katalin, Rigó Zita, Molnár Zsuzsanna, Dánielisz Ágnes, Takács Mária. Extraordinary increase in West Nile virus cases and first confirmed human Usutu virus infection in Hungary, 2018. Euro Surveill. 2019;24(28):pii=1900038. https://doi.org/10.2807/1560-7917.ES.2019.24.28.1900038
2. ECDC West Nile virus risk assessment tool. Available : https://ecdc.europa.eu/sites/portal/files/media/en/healthtopics/west_nile_fever/risk-assessment-tool/Documents/west-nile-risk-assessment-tool.pdf
3. ECDC Factsheet about West Nile virus infection. Available: https://ecdc.europa.eu/en/west-nile-fever/facts/factsheet-about-west-nile-fever
4. ECDC Weekly updates: 2019 West Nile virus transmission season. Available: https://ecdc.europa.eu/en/west-nile-fever/surveillance-and-disease-data/disease-data-ecdc
5. ECDC Technical report.West Nile Virus Risk assessment tool. Available: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/west-nile-virus-risk-assessment-tool.pdf

ANNEXES

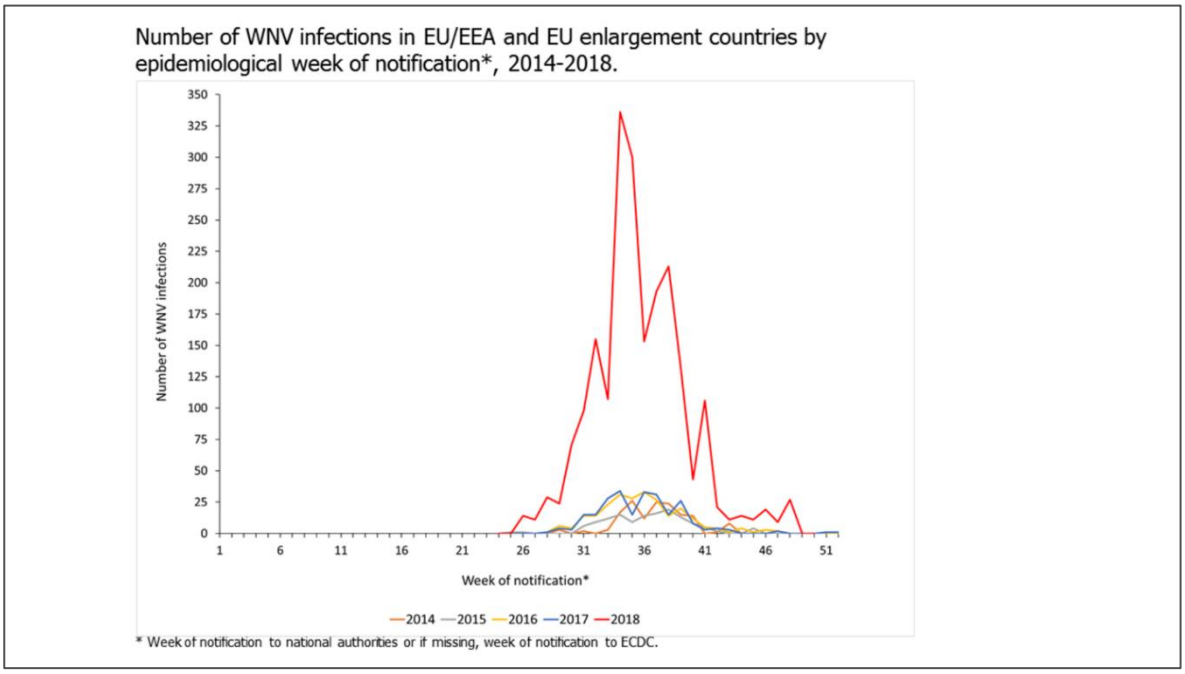
Annex 1: Information provided by Hungary on laboratory test results of the serum samples analysed for the WNV case with probable place of infection in Belgium

Sample	Test method	WNV IgM	WNV IgA	WNV IgG	USUV IgM	USUV IgA	USUV IgG	TBEV IgM	TBEV IgA	TBEV IgG
1st serum sample Sampling: 30/Jul/2018	IFA	1:10 weak pos	1:10 weak pos	1:1280 pos	<1:10 neg	<1:10 neg	1:80 weak pos	<1:10 neg	<1:10 neg	1:2560 pos
	ELISA	R=1.77 pos	commercial test is not available	R=2.78 pos	commercial test is not available	commercial test is not available	test kit is currently not available at our lab.	VE=5.61 neg	commercial test is not available	VE=48.26 pos
	HIA total antibody	≥1:1280			not tested			1:160		
2nd serum sample Sampling: 09/Aug/2018	IFA	1:40 pos	1:80 pos	1:5120 pos	<1:10 neg	<1:10 neg	1:640 pos	<1:10 neg	<1:10 neg	1:2560 pos
	ELISA	R=2.76 pos	commercial test is not available	R=3.49 pos	commercial test is not available	commercial test is not available	test kit is currently not available at our lab.	VE=5.56 neg	commercial test is not available	VE=61.9 pos
	Neutralization total antibody	≥1:126			not tested yet			not tested yet		

PCR: no viral nucleic acid could be amplified. (The NRL received only serum samples, neither whole blood, nor urine sample was available for PCR.)

- **Evaluated as a probable case of WNV infection.**

Annex 2: Number of WNV infections in EU/EEA and EU enlargement countries by epidemiological week of notification, 2014-2018 (source: ECDC)



Annex 3 : Distribution of West Nile virus infections in humans by affected areas in the EU/EEA Member states and EU neighbouring countries. Transmission season 2019 and previous transmission seasons. Last update 1st August 2019 (source: ECDC)