

Rapid communications

WHERE IS WEST NILE FEVER? LESSONS LEARNT FROM RECENT HUMAN CASES IN NORTHERN ITALY

F Gobbi (fgobbi@ulss20.verona.it)^{1,2}, G Napoletano¹, C Piovesan³, F Russo³, A Angheben², A Rossanese², A M Cattelan⁴, L Gallo⁵, M Valsecchi¹, A Piazza⁶, G Venturi⁷, Z Bisoffi²

1. Department of Prevention, ULSS 20, Verona, Italy

2. Centre for Tropical Diseases, Sacro Cuore Hospital, Negrar (Verona), Italy

3. Direction of Prevention, Veneto region, Venice, Italy

4. Unit of Infectious Diseases, Rovigo Hospital, Italy

5. Department of Prevention, ULSS 18 Rovigo, Italy

6. Unit of Microbiology and Virology, Padua Hospital, Italy

7. Department of Public Health, Local Health Unit, Ravenna, Italy

West Nile disease in humans has been detected for the first time in Italy in two regions, Emilia-Romagna and Veneto. Surveillance subsequently set up in Veneto detected a case of West Nile neuroinvasive disease and a few asymptomatic infections, but no case of West Nile fever. We conclude that also West Nile fever cases should be specifically targeted by surveillance.

Background

The first equine outbreak of West Nile virus (WNV) infections in Italy was reported in 1998 in Tuscany (province of Florence) [1]. Subsequent active human surveillance of stable workers identified four individuals who were seropositive but did not report any symptoms [2]. To our knowledge, no human passive surveillance (for ill people) was carried out in Italy at that time.

For the purpose of this paper, we define active surveillance as the active search for infected workers in stables who reported equine disease, while we define passive (rapid) surveillance as the screening for WNV disease among patients who seek medical care and fulfil the case definition (of suspected cases) outlined below.

Since 2001, a national veterinary surveillance system based on periodic testing of sentinel chickens and horses has identified sporadic seroconversions [3] without further occurrence of actual WNV disease until 2008 [4]. In August 2008, an equine WNV outbreak was detected in areas surrounding the Po river delta, involving the regions Emilia-Romagna (provinces of Bologna and Ferrara) and Veneto (province of Rovigo) (Figure 1). Subsequently, active and passive human surveillance was started in both regions [5].

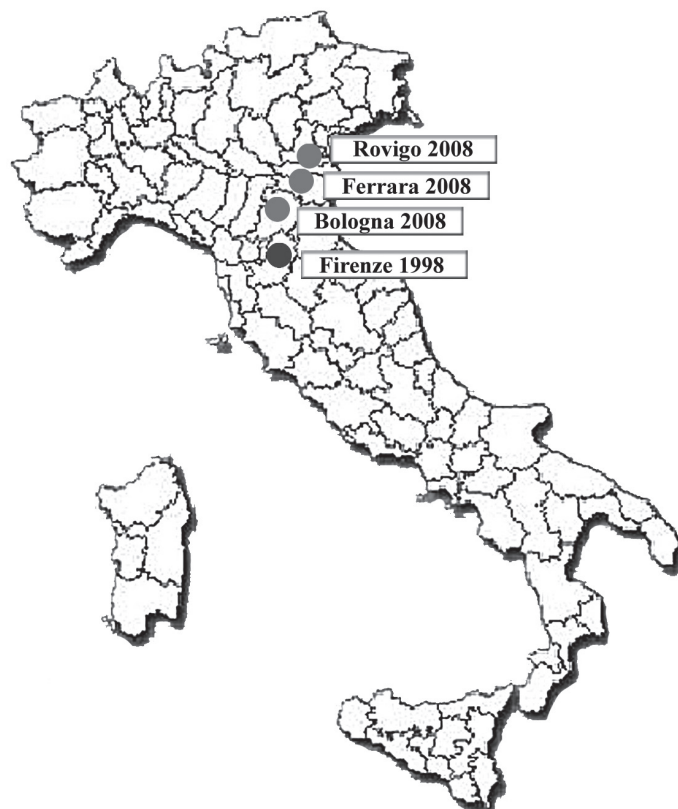
Case definition

West Nile fever is the most common clinical presentation of West Nile disease, and is characterised by a influenza-like, usually self-limiting febrile illness, usually accompanied by headache and joint and/or muscular pain, and sometimes by other non-specific symptoms including a maculopapular rash. West Nile neuroinvasive disease is a rarer, severe presentation characterised

by meningitis, encephalitis or infection of spinal motor neurons, with a high frequency of transient to permanent neurologic sequelae in survivors [6].

FIGURE 1

West Nile virus outbreaks in Italy, 1998 (horses) and 2008 (horses and humans)



The case definition of suspected cases (passive surveillance) was the same in both regions and specifically applied to West Nile neuroinvasive disease, including patients aged 15 years and older, with fever ≥ 38.5 °C and neurological symptoms such as encephalitis, meningitis, Guillain-Barré syndrome or acute flaccid paralysis.

Cases were further classified as:

- possible: clinical symptoms and clear (aseptic) cerebrospinal fluid (CSF);
- probable: clinical symptoms and at least one of the following laboratory criteria: ELISA detection of IgM antibodies against WNV; seroconversion; fourfold increase of IgG antibodies in acute- and convalescent-phase serum samples (preferably with 15-20 days between the two samples);
- confirmed: clinical symptoms and at least one of the following laboratory criteria: isolation of WNV from blood or CSF; ELISA detection of IgM antibodies in CSF; positive RT-PCR in blood and/or CSF; ELISA detection of increasing levels of IgM and IgG antibodies against WNV, confirmed by neutralisation testing carried out at the reference laboratory of the Istituto Superiore di Sanità in Rome [5].

Asymptomatic WNV infection was defined by positive serology in individuals identified through active surveillance and reporting no clinical symptoms.

West Nile virus in the Emilia-Romagna region, 2008

In September 2008, the first human case of West Nile neuroinvasive disease in Italy was reported in an 83 year-old female resident of rural Emilia-Romagna (province of Bologna) [7]. In October, another two neuroinvasive cases were reported in the same region (province of Ferrara). To the best of our knowledge, no case of WNV fever was reported in this region (L. Venturi, personal communication).

West Nile virus in the Veneto region, 2008

Passive surveillance

In October 2008, human passive (rapid) surveillance in Veneto identified an 81 year-old female resident of the province of Rovigo who was hospitalised with viral meningoencephalitis. As of 11 March 2009, the patient remains hospitalised in critical condition.

Active surveillance

Four WNV asymptomatic infections were identified by active surveillance (see Table and Figure 2). All serologically confirmed cases were WNV infections reported retrospectively by active surveillance: when WNV disease in horses was known to have occurred in a given stable, all stable workers were contacted by the

regional health teams, asked to complete a clinical questionnaire, and serum samples were taken for laboratory analysis as outlined above.

Other

In November 2008, a 48 year-old female resident of the province of Rovigo spontaneously presented at the Centre for Tropical Diseases in Negrar (Verona) and reported a fever episode three months previously, accompanied by maculopapular rash, adenopathy and severe headache, the latter still incompletely resolved as of January 2009. The patient had fully recovered in February.

At the time of the acute episode she had not been tested. Serologic testing in November 2008 (ELISA and neutralisation test) confirmed her as a case of WNV fever. As this case was identified neither by active nor by passive (rapid) surveillance, it is classified in the Table below as "other".

In February 2009, a second, probable human case of West Nile neuroinvasive disease in the same province in Veneto was identified retrospectively (highly positive IgG, ELISA test), although a positive PCR for Epstein-Barr virus in the CSF casts some doubts on this case. Laboratory confirmation is still pending, and the case is not included in the Table.

Discussion

In both Emilia-Romagna and Veneto, human surveillance was initiated once veterinary surveillance had identified the first cases in horses in August, 2008. Active surveillance targeted workers of infected stables, while passive (rapid) surveillance concerned suspected cases.

Not surprisingly, surveillance (in both Veneto and Emilia-Romagna) only detected either asymptomatic cases (active surveillance) or neurological cases (passive surveillance). West Nile fever cases were not reported, although this is by far the most frequent presentation of the disease. According to the literature, about 80 of 100 WNV infections are virtually asymptomatic, 20 are cases of West Nile fever, while the neuroinvasive disease accounts for less than 1% [6].

A major shortcoming of the current surveillance system is the concentration on neurological disease. Once animal or human cases have been detected, passive surveillance in humans should be broadened to include not only neurological disease, but also West Nile fever cases, in order not to miss the true extent of an outbreak.

The clinical picture of West Nile fever consists of fever with a variable combination of accompanying symptoms [6]. The case definition of a suspected case should therefore include any

TABLE

Individuals screened by active and by passive (rapid) surveillance for West Nile virus in the Veneto region, Italy, August 2008-March 2009

Type of surveillance	Screened	Positive asymptomatic	Positive for West Nile fever	Positive for West Nile neuroinvasive disease	Negative
Active	231	4			227
Passive (rapid)	7			1	6
Other	6		1		5
Total	244	4	1	1	238

unexplained fever, with or without rash, headache, adenopathy or joint pain, occurring in areas where veterinary disease is reported. Any more specific definition would not be sensitive enough to detect most cases.

Although West Nile fever is a benign disease, many reasons would justify making passive human surveillance as sensitive as possible during an outbreak. Firstly, the potential risk involved for blood transfusions [8] and transplantations [9] is not negligible: although viraemia roughly coincides with fever, and febrile patients would be suspended from blood or transplant donation in any case, effective surveillance of fever would better identify the geographic areas where human cases occur and where precautionary restrictions should be introduced. Secondly, West Nile fever itself may be a more severe illness than had previously been thought and recovery may require more than two months [6]: although there is no specific treatment to be offered, it is important to reassure the patients with regard to the cause of their complaints.

In summary, experience from the recent outbreaks highlights a need to review the current surveillance system for WNV. Timely diagnosis and reporting not only of cases of West Nile neuroinvasive disease, but also of West Nile fever cases would allow a more accurate assessment of the geographic distribution of WNV infection and guide control measures [10].

References

1. Autorino GL, Battisti A, Deubel V, Ferrari G, Forletta R, Giovannini A, et al. West Nile virus Epidemic in horses, Tuscany Region, Italy. *Emerg Infect Dis.* 2002;8(12):1372-8.

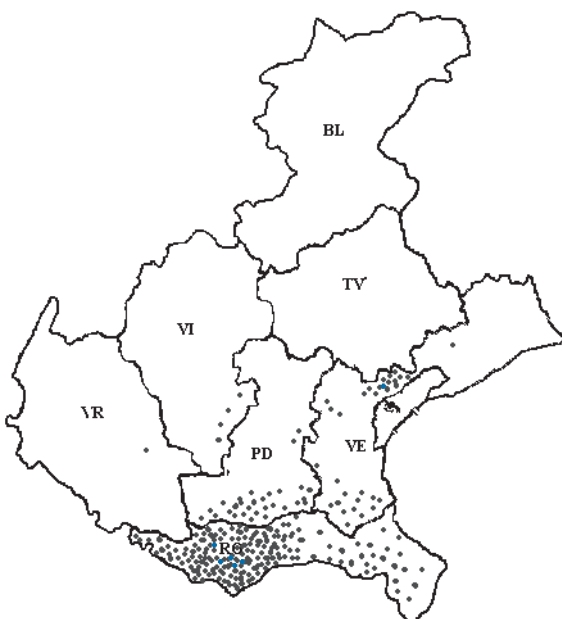
2. Direzione Generale della Prevenzione. Sorveglianza delle infezioni da virus West Nile in Italia. Circolare n. 400.3/3.2/ 4234. [General Directorate for Prevention. Surveillance of West Nile virus infection in Italy. Circular No. 400.3/3.2/ 4234]. Available from: www.ministerosalute.it/imgs/C_17_normativa_355_allegato. [In Italian].
3. Rizzoli A, Rosà R, Rosso F, Buckley A, Gould E. West Nile Virus Circulation Detected in Northern Italy in Sentinel chickens. *Vector-Borne and Zoonotic Diseases.* 2007;7(3):411-7.
4. Savini G, Monaco F, Calistri P, Lelli R. Phylogenetic analysis of West Nile virus isolated in Italy in 2008. *Euro Surveill.* 2008;13(48):pii=19048. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19048>
5. Macini P, Squintani G, Finarelli AC, Angelini P, Martini E, Tamba M, et al. Detection of West Nile virus infection in horses, Italy, September 2008. *Euro Surveill.* 2008;13(39):pii=18990. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18990>
6. Hayes EB, Sejvar JJ, Zaki SR, Lanciotti RS, Bode AV, Campbell GL. Virology, Pathology, and Clinical Manifestations of West Nile Virus Disease. *Emerg Infect Dis.* 2005;11(8):1174-9.
7. Rossini G, Cavrini F, Pierro A, Macini P, Finarelli A, Po C, et al. First human case of West Nile virus neuroinvasive infection in Italy, September 2008 - case report. *Euro Surveill.* 2008;13(41):pii=19002. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19002>
8. Grazzini G, Liumbruno GM, Pupella S, Silvestri AR, Randi V, Pascarelli N, et al. West Nile virus in Italy: a further threat to blood safety, a further challenge to the blood system. *Blood Transfus.* 2008;6(4):235-7.
9. Nani Costa A, Grossi P, Porta E, Venettoni S, Fehily D. Measures taken to reduce the risk of West Nile virus transmission by transplantation in Italy. *Euro Surveill.* 2008;13(42):pii=19009. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19009>
10. Watson JT, Pertel PE, Jones RC, Siston AM, Paul WS, Austin CC, et al. Clinical characteristics and functional outcomes of West Nile Fever. *Ann Intern Med.* 2004;141(5):360-5.

This article was published on 12 March 2009.

Citation style for this article: Gobbi F, Napolitano G, Piovesan C, Russo F, Angheben A, Rossanese A, Cattelan AM, Gallo L, Valsecchi M, Piazza A, Venturi G, Bisoffi Z. Where is West Nile fever? Lessons learnt from recent human cases in northern Italy. *Euro Surveill.* 2009;14(10):pii=19143. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19143>

FIGURE 2

Serology results (positive in blue, negative in gray) in the provinces of Veneto, Italy, August 2008-March 2009



RO: Rovigo; VR: Verona; VI: Vicenza; PD: Padova; VE: Venezia; TV: Treviso; BL: Belluno