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**REVIEW ARTICLE**

# West Nile virus infections in South-eastern Europe and in the Eastern Mediterranean area

Giovanni Rezza

*Department of Infectious, Parasitic and Immunomediated Diseases Istituto Superiore di Sanità, Roma, Italy*

**ABSTRACT**

The West Nile virus (WNV) was identified in Uganda in 1937. This virus appeared in the Mediterranean area in the early 1950s, causing an outbreak in Egypt. Since then, WNV caused a series of outbreaks, in human and/or horses, especially in North-Africa and in the Middle East. In the last few decades, the lineage 1 of West Nile started to cause sporadic cases and outbreaks of West Nile fever and neuroinvasive disease in Southern and Eastern Europe, and a large outbreak was reported in Romania in 1997; then, sporadic cases continued to be reported in central and southern Europe for years. Since 2010, West Nile has reemerged in Europe and in the Mediterranean area. Studies of molecular epidemiology show a co-circulation of WNV lineage 1 and lineage 2 in several European countries. In particular, WNV lineage 2 appears now to be established in South-eastern Europe and in the Balkans. This suggests that WNV is continuously reintroduced in this geographical area. Specifically, the two lineages of WNV are dispersed throughout Europe after arriving through bird migration, following the western and the eastern routes. The latter route is likely to be involved in the emergence and reemergence of WNV infection in South-eastern Europe, where this viral infection represent an important public health challenge. *J Microbiol Infect Dis 2014; Special Issue 1: S10-S16*

**Key words:** West Nile virus infections, South-eastern Europe, Eastern Mediterranean area, Emerging Infectious Diseases

## Güney-batı Avrupa ve Doğu Akdeniz Bölgesinde Batı Nil Virüsü Enfeksiyonları

**ÖZET**

Batı Nil virus (WNV) etkeni ilk olarak Uganda'da 1937 yılında identifiye edilmiştir. Bu virus 1950 yıllarının başında Mısır'da yaptığı salgınla birlikte Akdeniz bölgesinde kendini göstermiştir. O tarihten itibaren WNV özellikle Kuzey Afrika ve Orta-Doğu bölgesinde insan ve/veya atlarda birtakım salgınlara sebep olmuştur. Son bir kaç dekad içerisinde ise WNV-lineage 1 Güney Doğu ve Doğu Avrupa'da Batı Nil Virüs ateşi ve nöroinvazif hastalık şeklinde bir takım sporadik vakalar ve salgınlara sebep olmaya başlamıştır. Romanya'da 1997 yılında büyük bir salgın yaşanmış olup orta ve güney Avrupa'da yıllardır rapor edilmeye devam etmiştir. Son olarak 2010 yılından itibaren, Batı Nil Virüs enfeksiyonları Avrupa ve Akdeniz ülkelerinde yeniden önem kazanmıştır. Moleküler epidemiyoloji çalışmaları birçok Avrupa ülkesinde "WNV lineage 1 ve lineage 2'nin varlığını göstermiştir. Özellikle, WNV lineage 2'nin Güney doğu Avrupa ve Balkan ülkelerinde günümüzde dolaşmakta olduğu gözükmektedir. Bu WNV'nin sürekli olarak bu coğrafik bölgelerde yeniden önem kazandığını düşündürmektedir. Spesifik olarak, iki WNV türünün batı ve doğu yollarını takiben kuş göçleriyle birlikte tüm Avrupa'ya dağılmaktadır. Doğu hattı boyunca gerçekleşen kuş göçlerinin Güney doğu Avrupa'da önemli bir halk sağlığı problemi haline gelen WNV enfeksiyonlarının ortaya çıkması ve yeniden önem kazanmasında muhtemelen rol oynadığı değerlendirilmektedir.

**Anahtar kelimeler:** Batı Nil virus infeksiyonu, Güney-doğu Avrupa, Doğu Akdeniz Bölgesi, Yeniden önem kazanan enfeksiyon hastalıkları

## BACKGROUND

The West Nile virus (WNV) is a mosquito-borne flavivirus belonging to the Japanese Encephalitis complex. The virus was firstly identified in 1937 in a febrile patient in northern Uganda.[1]

Birds (i.e., waterfoul, passeriformes and columbiformes, plus many synanthropic birds) are the natural reservoir of the WNV, which is transmitted by mosquitoes of the Culex genus. The virus is maintained in a sylvatic cycle, probably by transmission

**Correspondence:** Giovanni Rezza, Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299 - Area Code 00161 Rome, Italy Email: giovanni.rezza@iss.it
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through Culex modestus mosquitoes, and in a urban cycle, through Culex pipiens, a highly ornithophilic species, which is abundant in urban areas and is a major epizootic vector among birds.[2,3] Horses and humans are only accidental dead-end hosts.

The genome of this single-strand RNA virus encodes for a single polyprotein which is then processed by viral and cellular proteases, in order to produce three structural (capsid, C; membrane, M; and envelope, E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5).[4]

From a phylogenetic point of view, two lineages of WNV have so far been described (3). The lineage 1 is widespread and further segregates into different subclades (1a-c): WNV-1a, which includes strains from all over the world, the Australian Kunjin (1b), and some Indian strains (1c) 5, whereas lineage 2 is mainly present in sub-Saharan Africa and has only recently been detected also in Europe. Other rare lineages have been identified (lineage 3 represented by a single isolate from Czech Republic, lineage 4 in Southern Russia, and lineage 5 in India, plus other putative lineages).6

WNV infection is often asymptomatic, causing a febrile syndrome in about 20% of the cases; West Nile fever (WNF) may be accompanied by a roseolar or maulopapular skin rash in up to half of the patients. In less than 1% of the cases WNV infection may cause a neuroinvasive disease (WNND), with a variety of symptoms such as high fever, severe headache, stiff neck, disorientation or confusion, stupor or coma, tremors or muscle jerking, lack of coordination, convulsions, pain, partial paralysis or sudden weakness.[2,7,8] Age-specific attack rates of WNND and fatality/case ratios tend to increase with age as a consequence of increased host susceptibility.[3]

WNV is widely distributed over the world. Beyond its original ecological niche in sub-Saharan Africa, WNV has been identified in Northern Africa, Europe, Asia, Australia[9], and, since the summer of 1999, in North-America.[10,11]

## WNV distribution in South-Eastern Europe and in the Mediterranean basis

In the Mediterranean area, WNV was first identified in Egypt in the early 1950s, and then caused a series of outbreaks, in human and/or horses, especially in North-Africa and in the Middle East.[8] Figure 1 shows the place and year of emergence of the main WNV outbreaks occurred in the Mediterranean basin and in the Balkans.

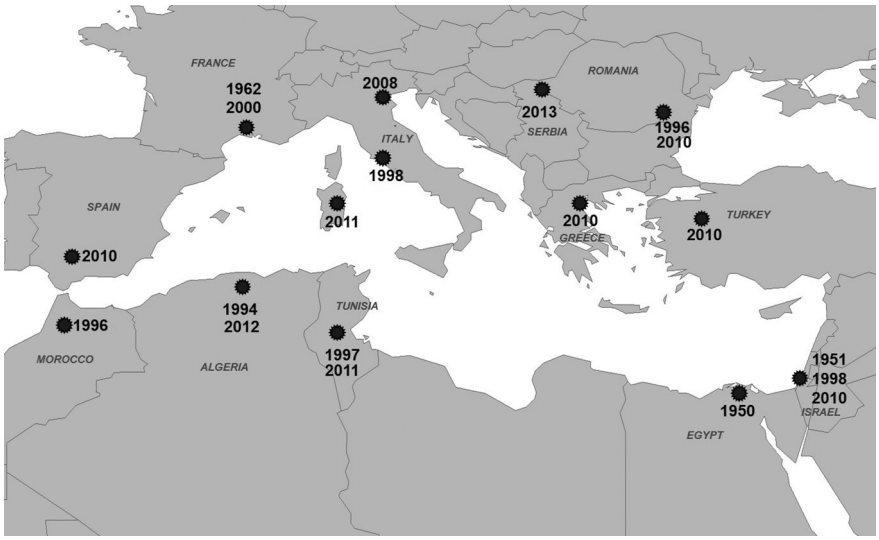


**Figure 1.** Main WNV outbreaks reported in the Mediterranean area: place of occurrence and year of identification.

In Europe, specific antibodies against WNV were detected for the first time in 2 Albanians in 1958.12 In 1963, WNV was isolated from humans and mosquitoes in the Rhone Delta (13), and from humans and Hyalomma marginatum in the Volga Delta.[14,15] Since the 1960s, WNV outbreaks occurred in several European countries, such as Southern France, Southern Russia, Spain, Romania, Belarus, and Czech Republic.[8]

However, WNV was only sporadically detected in humans until 1996, when a major outbreak characterized by a high fatality rate (~10%) occurred in Romania.[3,9] Since then, the virus has been isolated from horses, humans, and mosquitoes, in a number

of Eastern and Western European countries.[16,17] In particular, with the exception of an outbreak among horses in Camargue, Southern France, in the year 200018, and few cases detected in Spain[19] and north-Africa[20], WNV activity in Europe has been mostly concentrated in Italy and in south-eastern and eastern Europe (i.e., sporadic cases have occurred in Hungary every year, whereas large outbreaks have been reported in Russia).

Hereby we concentrate the attention on the Balkan and bordering countries (i.e., Italy, Romania and Turkey) and on the Eastern Mediterranean area.

## ROMANIA

Between mid-July and mid October 1996, 393 cases of WNND (352 cases) and WNF were reported in Romania. The outbreak was confined to Bucharest and to the lower Danube valley, with higher rates in the capital city. At the end of the outbreak, a seroprevalence of anti-WNV antibodies of 4.1% was estimated. Culex pipiens mosquito was the most likely vector of WNV.[3] Case-control studies identified "mosquitoes" in the home and "flooded apartment building basements" as risk factors for WNV infection.[21]

Sporadic cases of WNND continued to be identified in consecutive years after the 1996 epidemic,[22,23] until a large outbreak of 57 cases occurred in 2010.[24]

## ITALY

In Italy, WNV was firstly identified, in the summer of 1998; overall, 14 horses residing in the Tuscany region developed neurological symptoms[25]; no human cases occurred during the outbreak, but seroepidemiological surveys identified 4 asymptomatic cases among individuals working with horses.[26] The virus re-emerged in 2008 in the North-East of the country; since then, sporadic cases and/or clusters of West Nile neuroinvasive disease (WNND) among humans and horses continued to occur every year during the summertime.[27-30] Up to now, human cases of WNF or WNND have been reported in 4 regions of the North (Veneto, Friuli Venetia Giulia, Emilia-Romagna, and Lombardy), in 2 regions of the South Puglia and Basilicata), and in the Sardinia island.

### Greece and other Balkan countries

During 2010, Greece experienced the second largest outbreak of WNV infection since the one which occurred in Romania in the summer of 1996. Overall, 262 cases were reported, mostly in the Central Macedonia region.[31,32] In 2011 and 2012, 69 and 161 cases were identified, also from areas that had not been affected before. The reoccurrence of human cases in two consecutive years suggests that WNV is established in the country.[32,33] As expected, WNV has reappeared in the summer season of 2013, causing 81 cases by September.[26]

Other Balkan countries have reported WNV cases over the last few years. In Albania, 1 to 2 cases were reported in 2010-2011, whereas few sporadic cases were reported in FYRM, Kosovo, Montenegro and Bulgaria in the last three years. In Serbia WNV was firstly identified in 2012, when 69 cases of disease were notified, and a new outbreak is occurring in 2013, with 238 cases identified up to the end of September.[33]

## TURKEY

Cases of WNND and/or WNF were identified between 2010 and 2012 in several areas of the country, such as eastern Thrace [34] and the city of Ankara[35]: moreover, WNV-RNA was found in the CSF of humans and in the buffy coat of horses in Central Anatolia.[36] Human cases of WNV infection were also identified in the Mesopotamia Region in 2009, Syria border of Turkey.[37] Overall, surveillance data show that few cases were reported in 2010 compared with 2011, when a total of 47 human cases of WN disease was reported in the country.[33,38] Serosurveys conducted in 2009, using the plaque reduction neutralization test (PRNT), found a prevalence of 0.56% and 0.80% among blood donors in Anatolia[39] and in Hacettepe, respectively.[40] However, none of 729 healthy blood donors from Ankara tested by PCR resulted positive for WNV sequences.[41] Although data on human disease suggest a first, unexpected, epidemic event, with a peak of cases in 2010, followed by a rapid decline in the following year, studies conducted in the first half of the 2000s show the presence of neutralizing antibodies to WNV in a wide range of mammals and in up to 20% of humans, suggesting previous virus circulation.[42]

## MIDDLE EAST

Israel is apparently the most affected country in the Middle East, with over 100 cases reported in 2010 and recurrence of outbreaks in the following years. Human cases of WNF have been reported in Israel since the early 1950s, when several outbreaks

occurred; large outbreaks were also reported in 1980.[43] In the district of Tel Aviv, cases of WNND and WNF were notified every year in the period 2005-2010; incidence peaks observed in 2005 and 2010 were attributed to either the emergence of new virus variants or to extremely hot summer.[44] Sporadic cases of WNV infection have been also reported in the Occupied Palestinian Territory, whereas no human cases have been identified in other Eastern Mediterranean countries such as Syria, Lebanon or Egypt.[33,45]

**Molecular epidemiology and phytogeography of WNV**

WNV lineage 1, clade 1a, has been largely predominant in Europe and in the Mediterranean basin for a long time.

WNV strains belonging to lineage 1 have been identified over the years in Israel.[44] The large outbreak occurred in Romania in 1996 was also caused by WNV lineage 1.[46] Moreover, lineage 1 strains were detected also in Hungary[47] and were responsible of sporadic cases and outbreaks occurred among humans and animals in northeastern Italy between 2008 and 2012.[48-51] Finally, this lineage was isolated in Turkey, specifically in Thrace, in 201234 and in central Anatolia.[36]

The spatiotemporal distribution of WNV lineage 1 suggests that the virus was introduced from Africa to Europe by birds migrating through different routes (see Figure 2). In fact, microorganisms infecting birds tend to be dispersed along migration routes. WNV lineage 1 originated somewhere in Africa and was exported northward, mainly through the eastern route connecting Israel with central Europe and Russia. Another subSaharan strain spread to Morocco and the Maghreb, then entered Europe through Spain and possibly Italy, following the "Western route".

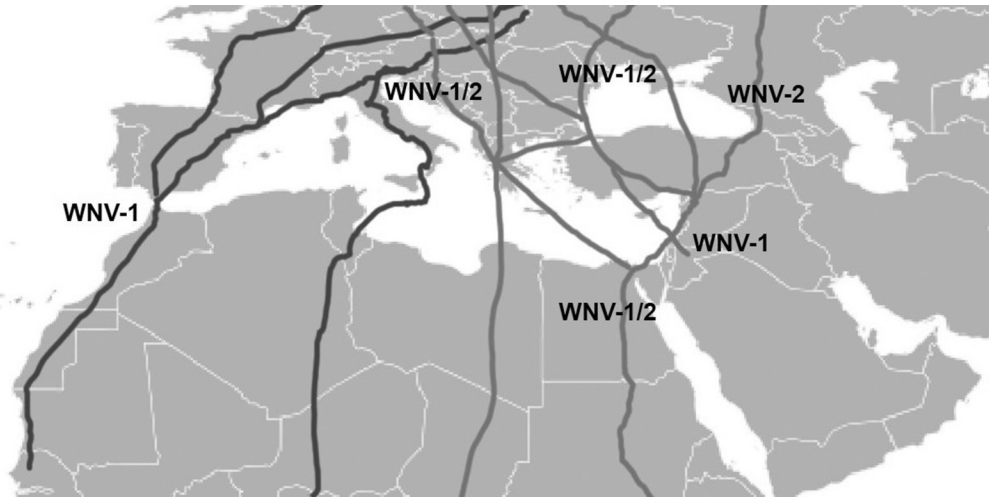


**Figure 2.** Bird migration routes and dispersion ways of WNV lineage 1 and 2.

WNV lineage 1a includes two different subclades: A and B. Subclade A, predominant in the Western Mediterranean area, has been detected also in Eastern Europe (i.e. Rumania and Volgograd, Russia), whereas the subclade B includes several strains which have been circulating in Israel (from where it was introduced into the United States of America) and in Eastern Europe.[52] Since the eastern-European isolates are included in at least two different clades, it is likely that the virus was reintroduced several times in Eastern Europe, probably following different bird migration routes.

The lineage 2 of WNV, which was probably introduced in Europe at the beginning of the years 2000s, is now predominant in several areas of the continent, in particular in Eastern and south-eastern Europe.

WNV Lineage 2 was isolated for the first time outside Sub-Saharan Africa in 2004, in a goshawk, in Hungary.[47] Interestingly, a lineage 1 strain had been isolated in a flock of geese in the same area in 2003, suggesting co-circulation of two different lineages in central Europe.[47] Since then, viral infections due to WNV lineage 2 have been identified in humans affected by WNF or WNND, in horses, birds, and mosquitoes. Large outbreaks of WNV disease in humans were identified in Russia, in the area of Volgograd, in 2007 and then in 2010-2012.[53] Surprisingly, WNV lineage 2, similar to the one isolated in Volgograd, was detected in 2010 in Roma-

nia, where all previous outbreaks had been due to lineage 1.[24] In Greece, large human outbreaks due to WNV lineage 2 occurred since 2010; viral sequences were obtained from Culex pipiens mosquitoes trapped in the town of Athanasios, west of Thessaloniki, on June 2011.[54] The enzootic circulation of WNV lineage 2 was confirmed by the detection of this strain among wild birds and chickens.[55,56]

In Italy, where the lineage 1 of WNV was responsible for all cases up to 2011, lineage 2 was firstly detected in two patient, one from central-eastern Italy and one from north-eastern Sardinia.[57,58] Unexpectedly, almost all cases of WNND and WNF identified in 2013 were caused by the lineage 2.[59]

Long-distance migratory birds overwintering in central Africa are likely having introduced WNV lineage 2 in Eastern Europe, starting from the wetlands of Hungary at the turn of the century. This virus lineage probably arrived following the eastern route, expanding its geographic range of activity within Europe, to Austria, Italy, and in particular to Greece, where large outbreaks occurred since 2010. To this regard, short-distance migratory birds are likely to play a role in virus migration within Europe.[6]

Phylogenetic analysis of eastern European strains suggests the introduction of a slightly different strain of WNV-2 to the Volgograd region of Russia at the beginning of the years 2000s; this appears consistent with an alternative route, which overlaps with the eastern flyway till Israel, where it turns towards the Black Sea and the Russian steppes.[6]

**Implications for South-eastern Europe**

In summary, the two main lineages of WNV are continuously reemerging in south-eastern Europe and in the Mediterranean basin, as shown in Figure 3. Viral reintroduction, especially of WNV lineage 2, appears to occur more frequently through the eastern route of bird migration; as a consequence, south-eastern Europe appears at high risk for WNV outbreaks. However, the impact of WNV disease appears to vary largely among different countries and within the country in the same European Region. Whether there are ecological factors which may explain such differences, including the influence of climatic changes, needs to be further investigated. Recently, the lineage 2 of the WNV has become predominant in European countries, and it seems to be the unique cause of ongoing outbreaks in south-eastern Europe, with particular regards to Greece and other Balkan countries (see Table 1). In other areas, co-circulation of two different lineages appears to occur. Whether the seasonal reoccurrence of sporadic cases and outbreaks of WNV may be due to continuous reintroduction of the virus or to the establishment of an enzootic cycle, due to virus overwintering in natural hosts (i.e., non-migrant or short distance migrant birds) or in infected mosquitoes, needs to be better defined. In fact, even though the co-circulation of different WNV lineages and the detection of viral diversity within the same lineage support the hypothesis of viral reintroduction, the detection of similar viral strains across the years suggests that virus overwintering in birds and/or in mosquitoes may also play a role.

**Table 1.** Characteristics of WNV outbreaks in South-eastern Europe and in the Eastern Mediterranean area

| Country | Year of activity | Lineage | Max N. human cases (Source. ECDC) |
|---|---|---|---|
| Albania | 2011 | 2 | 2(2011) |
| Bosnia-Herzegovina | 2013 | - | 1 (2013) |
| Bulgaria | 2012 | - | 2 (2012) |
| Croatia | 2012-2013 | - | 14 (2013) |
| Macedonia (FYRM) | 2011-2013 | - | 6 (2012) |
| Greece | 2010-2013 | 2 | 262 (2010) |
| Montenegro | 2013 | - | 2 (2013) |
| Kosovo | 2012 | - | 4 (2012) |
| Romania | 1996-1997<br>2010-2013 | 1<br>2 | 393 (1996)<br>57 (2010) |
| Serbia | 2012-2013 | 2 | 238 (2013) |
| Turkey | 2010,2 011 | 1 | 47 (2010) |
| Israel | 1951/1980<br>1998-2013 | <br>1 | N/A<br>435 (2000), 114 (2010) |
| Palestine (OPT) | 2012 | - | 2 (2012) |

FYRM: Former Yugoslavian Republic of Macedonia, OPT: Occupied Palestinian Territory

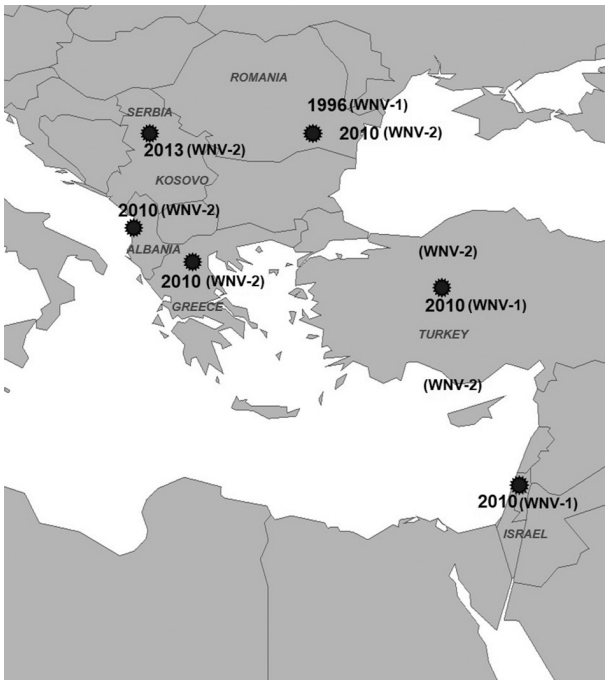


**Figure 3.** WNV outbreaks: date of notification of the first case and virus lineage involved in the outbreak/human cases.

In conclusion, Mediterranean and Middle-East countries, along with countries located in the Balkan inlands, have been dealing with recurrent seasonal outbreaks of WNV in the last few years. This urges a coordinated and appropriate public health response. Preparedness plans aimed at improving surveillance, diagnosis, treatment and control of WNV is an essential tool for reducing the burden of infection and disease in this geographic area.

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