Eur J Clin Microbiol Infect Dis (2004) 23:147–156
DOI 10.1007/s10096-003-1085-1

REVIEW

H. G. Zeller · I. Schuffenecker

West Nile Virus: An Overview of Its Spread in Europe and the Mediterranean Basin in Contrast to Its Spread in the Americas

Published online: 19 February 2004

Abstract West Nile (WN) virus is a mosquito-transmitted flavivirus. It is widely distributed in Africa, the Middle East, Asia, and southern Europe and was recently introduced to North America. Birds are involved in the cycle of transmission as amplifying hosts. Humans and horses are considered accidental dead-end hosts. WN fever was initially considered a minor arbovirosis, usually inducing a nonsymptomatic or a mild flu-like illness in humans, but some cases of encephalitis associated with fatalities were reported in Israel in the 1950s. After two silent decades, several human and equine outbreaks of fatal encephalitis occurred from 1996 to 2000 in Romania, Morocco, Tunisia, Italy, Russia, Israel, and France. In Romania, a few cases of WN encephalitis in humans are noticed every year, and in France, recent WN infections have been detected in monitored sentinel birds in 2001 and 2002. Phylogenetic studies have shown two main lineages of WN strains. Strains from lineage I are present in Africa, India, and Australia and are responsible for the outbreaks in Europe and in the Mediterranean basin, and strains from lineage II have been reported only in sub-Saharan Africa. In 1998, a virulent WN strain from lineage I was identified in dying migrating storks and domestic geese showing clinical symptoms of encephalitis and paralysis in Israel. A nearly identical WN strain suddenly emerged in New York in 1999, killing thousands of native birds and causing fatal cases in humans. The virus is now well established in the New World, and it disseminates rapidly. New modes of transmission through blood donations, organ transplants, and the intrauterine route have been reported. In Europe, an enhanced surveillance of WN infection in humans, horses, birds, and vectors may reveal the presence of the virus in different locations. Nevertheless, outbreaks of WN virus remain unpredictable. Further coordinated studies are needed for a better understanding of the ecology and the pathogenicity of the WN virus.

H. G. Zeller (✉) · I. Schuffenecker
Institut Pasteur,
National Reference Center for Arboviruses,
21 Avenue Tony Garnier, 69365 Lyon Cedex 07, France
e-mail: zeller@cervi-lyon.inserm.fr
Tel.: +33-4-37282421
Fax: +33-4-37282451

Introduction

West Nile (WN) fever is a viral disease originally identified in Africa in the West Nile district in Uganda [1]. The viral agent was isolated in 1937 from the blood of a febrile patient and was found to be antigenically related to the virus that causes Japanese Encephalitis [2]. Other isolates were later obtained from the blood of apparently healthy children in Egypt [3]. Ecological studies undertaken in 1952–1954 in the Sindbis district in Egypt established the cycle of the virus, which involves mosquitoes as vectors, birds as amplifying hosts, and humans and horses as sensitive dead-end hosts [4, 5]. The virus was recovered from mosquitoes, birds, and humans and had a widespread geographical distribution in Africa, Europe, and Asia [6].

Initially, WN fever was considered a minor arbovirosis, inducing in humans essentially a nonsymptomatic disease or a mild flu-like illness. The first epidemics of encephalitis were reported in Israel in the 1950s and then in France in 1962–1963, affecting both humans and horses [7, 8]. Three fatal cases in children were described in India [9]. More recently, WN fever has become a major public health and veterinarian concern. During the last 10 years, several human outbreaks have been reported in the Mediterranean basin and southern Europe, with fatal cases of encephalitis occurring principally among elderly people. Outbreaks have occurred in Algeria in 1994, Romania in 1996, Tunisia in 1997, Russia in 1999, and Israel in 2000 (Fig. 1) [7, 10]. Epizootics in horses have also been described in Morocco in 1996, Italy in 1998, and France and Israel in 2000 (Table 1) [11, 12, 13, 14]. In 1998, in Israel, an unusual mortality related to WN infection was observed in migrating white storks and domestic geese [15]. In all these different episodes, the period of detection of clinical cases started in July–

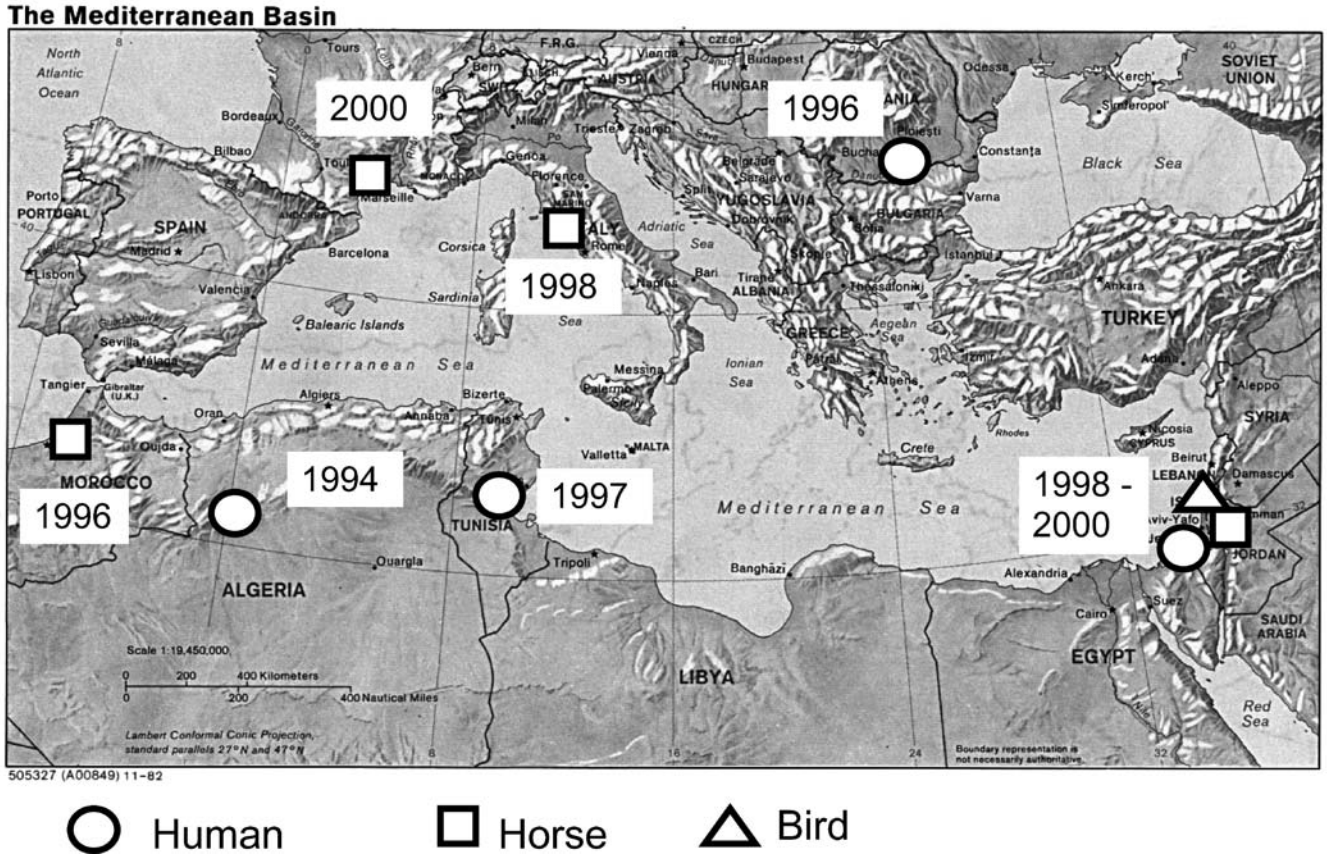

Fig. 1 Outbreaks of West Nile virus infections reported in the Mediterranean basin, 1994–2002

Table 1 West Nile outbreaks in Europe and the Mediterranean basin since 1994–2002

Year	Country	No. in humans		No. in horses		Date	Reference
		Cases	Deaths	Cases	Deaths		
1994	Algeria	50	2			Aug–Sept	[77]
1996	Morocco	1	1	94	42	Aug–Oct	[11]
1996	Romania	393	17			mid July–mid Oct	[70]
1997	Tunisia	173	8			Sept–Nov	[7]
1998	Italy			14	6	mid Aug–early Oct	[12]
1999	Russia	318	40			end July–Sept	[71, 72]
1999	Israel	2	2			end Aug	[20]
2000	France			76	21	mid Aug–early Nov	[13]
2000	Israel	417	35	76		Aug–Oct	[14, 39]
2000	Russia	56					[73]
2001	Russia	64	(5–10%)				[73]

August, in relationship to high temperatures and an active mosquito population. As a consequence of those outbreaks, surveillance programs of WN fever were initiated in Europe. Several encephalitis cases related to WN infection are diagnosed every year in Romania, mostly around the Danube delta [16]. WN virus activity, as indicated by isolations of the virus, is reported annually in the Volga delta (D.K. Lvov, personal communication). In France, some seroconversions in sentinel birds in 2001 and 2002 indicate a low enzootic maintenance of the virus in a previously infected area (unpublished data).

The unexpected emergence of WN virus during the summer of 1999 in New York City and its rapid spread throughout the USA underlined the ability of an arbovirus to become a major threat [17, 18]. Numerous fatalities were recorded in many resident birds [19]. The connection with the WN viral strain identified previously from birds in Israel was established [20]. Crows and blue jays were among the species most affected [21]. By the end of October 1999, the disease had already spread in four states. Then, the virus was recovered from overwintering mosquitoes and a dying hawk in February 2000 [22, 23]. From 1999 through 2001, there were 149 human cases

and 18 deaths due to WN infection reported from 24 states (Centers for Disease Control and Prevention statistics). In 2002, reported cases increased, with 4,156 laboratory-confirmed cases and 284 fatalities. As of 31 October 2003, more than 7,700 cases and 166 fatalities had been documented (CDC statistics). Only four U.S. states have not yet reported cases of WN infection in humans. A total of 738 equine cases were notified in 2001 and 14,717 in 2002. The virus also spread extensively throughout Canada; 13 provinces were reported infected by WN virus in August 2003 (Public Health Canada statistics).

The southward spread was noticed in 2001, with one human case of WN infection in the Cayman Islands and seropositive horses and/or resident birds detected in 2002 in Mexico, El Salvador, Jamaica, the Dominican Republic, and Guadeloupe [24, 25, 26, 27, R. Quirin, personal communication]. Besides the classical infection by mosquito bite, some unusual patterns of transmission were described: blood transfusion, organ transplantation, vertical transmission, and possible transmission via breast feeding [28, 29, 30].

Viral Structure and Taxonomy of West Nile Virus

WN virus particles are spherical and 50 nm in diameter, with an envelope and a single-stranded positive-sense RNA. The genome, 11,000–12,000 nucleotides long, has a single open-reading frame encoding 10 proteins: 7 nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) and 3 structural proteins (core C, membrane M, and envelope E) [31]. The E protein is implicated in the recognition of the viral receptor on the surface of the cell and in the induction of humoral immunity. Virus replication occurs in the cytoplasma in close association with the endoplasmic reticulum endothelium (ER) followed by viral assembly in the ER lumen and release from the cell by exocytosis.

WN virus belongs to the Japanese Encephalitis complex within the *Flavivirus* genus, which includes several human pathogens: Japanese Encephalitis virus in Asia, Murray Valley Encephalitis virus in Australia, and Saint-Louis Encephalitis virus in the Americas. This complex also includes Cacipacore virus from Brazil, Alfuy virus from Australia, and the Koutango, Usutu, and Yaounde viruses from Africa [32]. Kunjin virus, which was previously described in Australia, has been shown to be related to WN virus isolates in phylogenetic studies [32, 33]. All of these different viruses are transmitted mostly by *Culex* mosquitoes in a cycle involving birds as amplifying hosts. Specific antibodies to these viruses are reported in various vertebrates, including rodents [6].

Clinical Features and Pathogenesis of West Nile Virus Infection

The incubation period of WN virus infection is usually 3–15 days after the bite of an infected mosquito. Most of the cases of WN infection are nonsymptomatic. In 15–20% of the cases, mild flu-like illness is reported, generally characterised by an abrupt onset of fever, headache, myalgia, malaise, anorexia, nausea, and vomiting [34]. A maculopapular or roseolar rash may be observed. The disease may last 2–5 days. In less than 1% of the cases, neurological symptoms such as meningitis, meningoencephalitis, or myelitis appear, generally associated with high fever [35]. Other neurological presentations are ataxia and extrapyramidal signs, polyradiculitis, seizures, and eye nevritis [36, 37]. Muscle weakness is a prominent part of the clinical presentation of many patients with WN encephalitis [8, 35, 36]. In a very few cases, fulminant hepatitis, pancreatitis, and myocarditis have been reported in association with WN infection [38, 39, 40].

In the 1996 Romania outbreak, 352 patients presented with acute central nervous system infection: meningoencephalitis (44%), meningitis (40%), or encephalitis (16%) [41]. All 17 fatal cases were recorded in patients over 50 years of age. In the 2000 outbreak in Israel, the clinical features in hospitalised patients were encephalitis (58%), meningitis (16%), and febrile illness (29%) [42]. In the CSF, pleocytosis, predominantly with lymphocytes, elevated protein, and normal glucose, was commonly recorded. The median age of the 13 fatal cases was 80 years, ranging from 54 to 95 years [8]. Independent predictors of death were age over 70 years, change in the level of consciousness, and anemia [42].

Following the mosquito bite, the initial viral replication probably occurs in the closest regional lymph nodes. Virions produced can then reach the reticulo-endothelial system [31]. A second episode of viremia of short duration may follow in relationship with the onset of fever. In certain circumstances, WN virus enters the central nervous system and causes neurological disease by replicating in neuronal cells. WN virus consistently causes inflammation of the medulla, the brain stem, and the spinal cord with lymphocytic perivascular inflammation and formation of microglia nodules [40].

In horses, the disease is characterised mainly by ataxia, muscular weakness, and amaurosis [43]. In the French outbreak in 2000, among 131 horses with neurological signs, 76 had laboratory-confirmed infection and 21 died [44]. Among the 76 confirmed cases, ataxia was present in 72%, fever in 62%, and paralysis or paresis in 47% [44]. Additional serological investigation conducted in 5,133 horses in the Camargue region indicated that 504 (9.6%) animals had been infected without noticeable clinical symptoms [44]. Among 12 horses infected experimentally by *Aedes albopictus* mosquitoes infected with the NY strain, encephalomyelitis was recorded in only 1 horse. The other 11 horses had no clinical signs [45]. In another experimental assay, the most constant cerebral lesions were meningeal and submeningeal oede-

ma associated with lymphocytic perivascularitis [46]. During the 1998 equine outbreak in Italy, all dead animals showed histologically slight-to-moderate nonsuppurative encephalomyelitis, with lesions predominantly observed in the spinal cord and the lower brain stem [47].

In dying birds, gross haemorrhage of the brain, splenomegaly, meningoencephalitis, and myocarditis were the most prominent features [48]. Cellular targets included neurons and glial cells in the brain, spinal cord, and peripheral ganglia.

In other sensitive animal species, foci of nonspecific necrosis were observed in multiple organs [49].

Diagnosis of West Nile Virus Infection

Serological Diagnosis

The diagnosis of acute WN infection is based on the detection of specific IgM antibodies in serum and/or CSF using an immunocapture ELISA test and an increase in IgG titres between acute-phase and convalescent sera (Fig. 2). Usually, IgM-specific antibodies are detected when neurological symptoms appear [50], and the presence of IgM in CSF is associated with intrathecal viral replication. However, the IgM ELISA tests are not able to differentiate between the WN, Saint Louis Encephalitis, and Japanese Encephalitis viruses, which are closely related. Moreover, low titres of specific IgM have been reported in some patients for more than 12 months, attesting that the presence of IgM is not systematically associated with a recent infection [51]. So, in case of positive IgM results, it is necessary to confirm the diagnosis by a neutralisation test (plaque reduction neutralisation test), which is able to detect specific WN neutralising antibodies and to differentiate between closely related flaviviruses. Of note, the problem of cross-reactivity between flaviviruses still appears of little concern in cases of indigenous European WN infection in humans.

Direct Diagnosis

As the viremia in humans is classically low and short in duration (Fig. 2), WN virus has rarely been isolated from the serum or CSF of meningoencephalitis patients [51, 52, 53]. Isolation of the virus would require a blood sample collected early after the onset of fever or an abnormally lasting replication of the virus due to immunodepression. As in humans, viremia in horses is very low: 10^1–10^3 plaque-forming units (pfu)/ml for less than 6 days in horses experimentally infected by mosquito bite [44]. Reverse transcriptase (RT)-PCR methods of high sensitivity (0.1–1 pfu/ml) have been developed, but their utility is limited due to the transient nature of the viremia [54]. They should be applied very soon after the onset of clinical signs (Fig. 2). In fatal cases, the virus can be easily identified and isolated from a brain biopsy [9, 55].

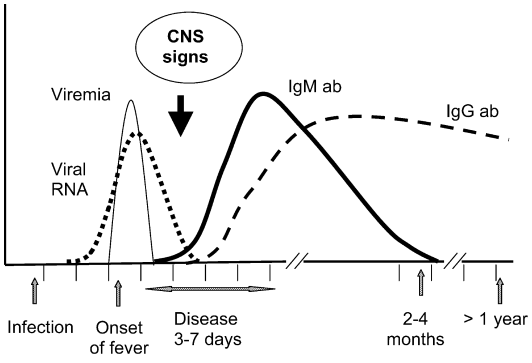

Fig. 2 Viremia and antibody kinetics in West Nile virus infection

Prevention of West Nile Virus Infection

Preventive measures in North America focus on the use of mosquito repellents. Mosquito control measures by large sprays of insecticides are not efficient, partly due to the large variety of mosquito populations involved in the cycle of transmission. There is no human vaccine available. Killed vaccines have been used in the USA in horses with a classical immunisation process: two initial intramuscular doses, 3–6 weeks apart, followed by a yearly booster. Recombinant DNA vaccine (pCBWN DNA) has been shown to be protective in horses, mice, and fish crows by intramuscular inoculation [56, 57]. Other approaches include the use of live attenuated vaccines, which induce rapid immunity after a single dose and strong and durable immunologic memory. Chimeric vaccines are under construction using the 17D yellow fever vaccinal strain as a vector and the prM and E genes of WN virus [58].

Viral Ecology of West Nile Virus

Mosquitoes

WN virus has been recovered from 11 genera of mosquitoes in Africa and America: *Culex*, *Ochlerotatus*, *Aedes*, *Anopheles*, *Coquilletidia*, *Aedemomyia*, *Mansonia*, *Mimomyia*, *Psorophora*, *Culiseta*, and *Uranoteania* [59, L. Petersen, personal communication]. In the Mediterranean basin, the virus was isolated in Israel, Egypt, and Algeria, mostly from *Culex* mosquitoes: *Culex antennatus*, *Culex univittatus*, and *Culex pipiens* [5]. In Europe, isolations from mosquitoes belonging to four genera have been reported in Portugal, France, Romania, the Czech Republic, southern Ukraine, Slovakia, and southern Russia [59, 60]. Only the mosquito species that replicate the virus and assure its transportation to the salivary glands via the haemolymph are potential competent vectors. Members of the *Culex* genus are thought to be the most efficient for spreading the virus among birds and from birds to humans and mammals [5]. Field evidence of natural vertical transmission of WN virus in *Culex*

mosquitoes was reported in Kenya and persistence of the virus in overwintering mosquitoes in North America [22, 61]. Furthermore, vertical transmission was also demonstrated experimentally [62, 63].

Birds

The study conducted in Egypt in the 1950s underlined the role of birds as amplifying hosts and was followed by experimental studies in South Africa [4, 64]. Some isolations from birds were reported in the Old World from native or migrant, aquatic, or terrestrial birds (crow, pigeon, turtle, duck, teal, gull, starling, sandpiper, coot, ibis, heron) in Egypt, Slovakia, Cyprus, Russia, and the Ukraine [57, 65, 66]. In Eilat (Israel) in September–October 1998, WN virus was isolated from several white storks (*Ciconia ciconia)* and domestic geese showing clinical symptoms of encephalitis and paralysis [15]. The emergence of WN virus in New York City was revealed by the death of thousands of native (crows, ravens, magpies, jays) as well as exotic birds [19, 23, 48]. Several species, including the blue jay, common grackle, house finch, house sparrow, and American crow, develop high viremia and are capable of infecting mosquitoes that feed on them [21]. Bird mortality has been a key indicator for following the spread of WN virus across North America.

Ticks

The possible role of ticks in the transmission of WN virus has been repeatedly reported [6, 59, 65]. WN virus was isolated from soft ticks Argasidae *Argas* species and from hard ticks Ixodidae *Hyalomma* species [6]. Adult *Argas* ticks artificially fed on bovine serum containing WN virus were able to transmit the virus to chickens 20 days later [67]. Vertical transmission was recorded in the progeny, and the larvae were able to transmit the virus. Ticks may play a substantial role in the geographic distribution and the maintenance of WN virus.

Mammals, Reptiles, and Amphibians

Isolation of WN virus has been reported in diverse animal species: yellow-necked mice and bank voles in Hungary, hares in southern Russia, and amphibians (frogs) in Tajikistan. The viremia in frogs was reproduced experimentally, with transmission of the virus to *Culex pipiens* mosquitoes [66]. Antibodies related to WN virus were detected in a large variety of mammals, including brown bears, boars, hares, and deer [59]. In North America, bats, cats, dogs, raccoons, rabbits, squirrels, chipmunks, mountain goats, reindeer, and alpacas were found positive for WN virus. Infection in a wolf pup, a dog, and farmed reptiles (alligators) was reported in the USA [49, 68]. Reptiles are potential amplifying hosts, as they are known to develop viremia of long duration, allowing the virus to survive over winter. They are involved in the cycle of other arboviruses like the Western Equine Encephalitis virus [69].

Epidemiology of West Nile Virus

In Europe, the circulation of WN virus in humans was assumed on the basis of serological surveys conducted in Albania, Portugal, Spain, Romania, and Slovakia in the 1960–1980s, particularly in biotopes of migratory birds [66]. The first recognised outbreak in Europe occurred in 1962–1963 in France, with encephalitis cases in horses and humans [7]. Neurological WN-related infections in humans were described in the western Ukraine in 1985 and then in southern Russia (Astrakhan region) in 1991–1996 [59, D.K. Lvov, personal communication]. From mid-July to mid-October 1996, a large outbreak of meningitis and encephalitis was reported in Romania [70]. A total of 393 cases were laboratory-confirmed, most (73%) of them in patients from the city of Bucharest (Table 1). There were 17 fatal cases, all in patients over 50 years of age. During the summers of 1997 and 1998, neurological infections were serologically diagnosed as WN encephalitis in 13 patients (1 fatal case). Most cases were reported from districts near the Danube delta. Meanwhile, sentinel chickens in Bucharest seroconverted for WN virus during the same period [16]. In 1999, WN virus infection was confirmed in 7 patients, including one who died; in 2000, 13 human cases were laboratory confirmed, including 2 that were fatal (C. Ceianu, personal communication). In the Czech Republic, sporadic cases were documented in 1997 [59]. Another severe outbreak occurred in the Volgograd region in Russia in 1999, with 40 fatalities. Most of the patients were from the cities of Volgograd and Volzskii [71, 72]. Among 380 patients with serologically confirmed infection, 288 (75.8%) had meningitis and 44 (11.6%) meningoencephalitis. In 2000, 20 cases with CNS involvement were reported in the Volgograd region, and there were 136 cases (5 deaths) in the city of Astrakhan in the years 1997–2000, mostly among residents of Astrakhan [73].

Epizootics in horses but an absence of symptomatic human cases were described in Italy in 1998 (14 cases) and in France in 2000 (76 cases) in the Camargue region [12, 13]. A low seroconversion rate has since been noticed in Camargue in sentinel birds (ducks and chickens) in 2001 and 2002. Such results indicate a low rate of transmission of WN virus between ornithophilic mosquitoes and birds without noticeable extension to sensitive hosts. In August 2001, the Usutu (USU) virus, which is related to WN virus, was isolated from dying Eurasian blackbirds (*Turdus merula*) in the Vienna area in Austria [74]. This virus is known to circulate in sub-Saharan Africa in mosquitoes and some bird species without having any clear pathogenicity in humans. Other birds died in 2002, indicating that the virus had likely survived over the winter [75]. In the southern UK (Cam-

bridgeshire), neutralising antibodies related to the WN and USU viruses have been recently detected in various resident species of birds, along with viral RNA linked to WN virus in some dead Corvidae [76]. These intriguing preliminary findings need further investigation.

In northern Africa, epidemics with clinical cases of encephalitis occurred in 1994 in the Timimoun Oasis in central Algeria and in 1997 in Tunisia in the Sfax and Mahdia districts [7, 77]. In Morocco in 1996, 42 horses and one man died following WN virus infection [11, 78]. In Israel in 2000, there was a large epidemic throughout the country: 417 patients were hospitalised, 328 of whom had laboratory-confirmed cases of WN fever and 35 of whom died (fatality rate=8.4%). All cases occurred in patients over 50 years of age [8]. Cases in horses also were reported [14]. Further cases were notified in 2001 and 2002, some of which were fatal.

Prior to 1997, WN virus was considered non-pathogenic for birds. In 1997–1998, in Israel, a more virulent strain was identified in dying migrating storks and other bird species, including raptors [15]. Flocks of domestic geese were infected in 1998, exhibiting clinical symptoms of encephalitis and paralysis [15, 79]. In contrast, mortality related to WN infection was not noticed in birds during the most recent outbreaks in Europe. WN virus suddenly emerged in New York during the summer of 1999, killing thousands of native birds from various species, mainly crows and blue jays; fatal cases in humans and horses also were reported. The virus was initially suspected to be the Saint-Louis Encephalitis virus but was rapidly determined to be WN virus. The rapid spread of the virus throughout the USA and Canada showed that the virus had found competent vectors, susceptible amplifying hosts, and efficient mechanisms for survival during the cold season [22, 23].

The virus is now well established in the New World, and mortality among birds has been a key indicator for WN surveillance [18]. Phylogenetic results indicated that the WN strain had been introduced from the Middle East, but the means of introduction is still under investigation. The introduction via insects or mosquitoes (eggs, larvae, adults) in containers on ships or airplanes is a sustainable assumption [20]. Another possibility is the legal/illegal introduction of infected birds into New York City. The introduction by humans is very unlikely due to the low viral levels in humans and the short duration of viremia. The hypothesis of introduction via migrating birds appears equally improbable. In 2002, 4,156 cases were confirmed, with 284 fatalities (fatality rate=6.3%) (CDC statistics). Due to previous observations in Romania in 1996–1997, where the estimated clinical-to-subclinical infection ratio was 1 to 140–320, it is assumed that more than 500,000 human infections had occurred in 2002, mostly during the period from the end of July to the beginning of September [70]. Some human cases of neurological WN infection imported from North America were reported in Europe and South Africa in 2002 and 2003 [80, 81]. In 2003, more than 7,700 cases and 166 fatalities were reported among humans in the USA as of 31 October (CDC statistics) and 1,300 probable or confirmed cases as of 4 November in Canada (Health Canada statistics). The main vectors seemed to be *Culex pipiens* in the northern USA and *Culex quinquefasciatus* in the southern USA, and possibly *Culex tarsalis* in the western USA (Lyle Petersen, personal communication).

The epidemiology of WN virus appears to have changed since the virus reached Mexico and the Caribbean region in 2002. In these areas, seroconversions in horses were noticed with very few clinical cases, along with seroconversions among resident birds without major fatalities and an absence of confirmed cases in humans [25, 26, 27]. The ecology of the virus is changing with the variations in mosquito populations and vector competence. Moreover, it is affected by competition due to the cocirculation of other arboviruses. Likewise, heterologous immunisation by other flaviviruses may induce partial protection against WN infection [82].

The large outbreak in 2002 revealed new modes of transmission through blood donations or organ transplantation from asymptomatic donors [28]. There were 23 cases believed to be related to blood transfusion in 2002. Nine of the 16 infectious donors had symptoms before or after blood donation, and 5 were nonsymptomatic [83, 84]. The classical picture of WN, with viremia occurring during the onset of fever, must be revised (Fig. 2). Meanwhile, one case of intrauterine WN virus infection was diagnosed on the basis of WN-specific IgM present in the mother and the baby [30]. The mother had a febrile illness estimated to have occurred in week 27 of pregnancy, and the baby had severe cerebral abnormalities. There was no proof of a causal relation between the infection and abnormalities. Blood products are now tested for WN virus by nucleic acid testing in the USA and Canada, a procedure that began in June 2003 [83]. In addition, blood banks are excluding donations from people who have had fever and headache in the preceding month. Several first incidences of infected donations were reported, even though no human cases were notified in the state of residency of the donor. In some European countries, recommendations for blood donation in 2003 include postponement for travellers to areas in the USA and Canada where human cases are reported [85].

Nevertheless, the risk of transmission of the virus remains low. Worldwide there are 50–80 million dengue infections every year, and dengue viral investigation is not performed on blood donations. Transmission of dengue via blood products may occur with a higher frequency, even if the probability of transfusion of blood from a viremic donor would be expected to be very low. The disease is common in endemic countries, with multiple infections caused by the four dengue serotypes, and such modes of transmission will be unnoticed.

Phylogenetic Studies and Genetic Susceptibility of West Nile Virus

Phylogenetic studies on a 255-bp region of the E glycoprotein gene (genome position 1402–1656) have shown the existence of two main lineages that diverge by up to about 30% in nucleotide sequence [33, 86]. Lineage I includes WN strains from Africa, Europe, the Middle East, North America, India, and Australia. Lineage II comprises WN strains only from sub-Saharan Africa and Madagascar (Fig. 3). The viral strains responsible for recent outbreaks in humans, horses, and birds belong to lineage I and show strong nucleotide sequence similarity (98–100%). One cluster included the recent strains from horses (Morocco/1997, Italy/1998, and France/2000), and another cluster included strains responsible for human deaths (Tunisia/1997, Israel/1998, and New York/1999) [10]. In Israel, the WN virus strain isolated from the brain of one patient in 1999 was nearly identical to the avian strain of 1998 [20]. Comparing a 1,648-nucleotide sequence encoding for the PreM gene, the M gene, and part of the E gene, studies have shown several strains of WN virus were cocirculating in Israel in 2000 [52]. One group is related to the previously identified strain from a bird in 1999 and another group is related to a human isolate from Russia (1999) and an isolate from *Culex pipiens* mosquitoes from Romania (1996). Additional studies demonstrated that 29 strains from South Africa, Namibia, Mozambique, and Botswana isolated from mosquitoes, humans, birds, dog, and horse belonged to lineage II [39].

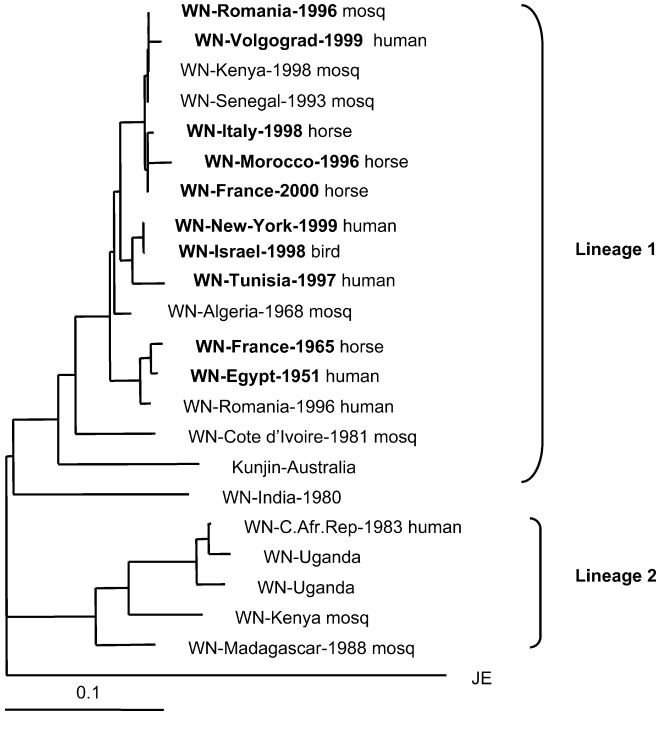

Fig. 3 West Nile virus phylogenetic tree based on nucleic sequence data of E-glycoprotein gene fragment of 245 bp

Although the phylogenetic studies are interesting in epidemiology for tracing the geographic dispersion of WN viruses, they do not explain the differences in pathogenicity between viral strains experimentally demonstrated in mice [87]. Meanwhile, recent studies on the genetic susceptibility of hosts to WN infection have identified a genetic allele that apparently confers susceptibility to flaviviruses in mice. 2'-5' oligoadenylate synthetases are interferon-inducible proteins that are known to play an important role in the antiviral pathway. A non-sense mutation in the exon 4 of the gene encoding the L1 isoform has been shown to be associated with susceptibility to WN infection, whereas all resistant mice have a normal copy of the gene [88, 89]. Further studies are underway to determine if the murine model is relevant in humans.

Conclusion

The occurrence of outbreaks of WN fever remains unpredictable, as recently observed with the limited outbreak in humans and horses in La Riviera, southern France, at the end of August 2003 [90]. The immediate adaptation of the WN virus in North America demonstrated the capacity of this arbovirus to disseminate. Persistent infections in some vectors and hosts may allow the virus to survive during the cold season. New introductions of WN virus in Europe may occur via unusual modes, requiring enhanced surveillance. There is a need for increased awareness among clinicians and veterinarians about the possibility of WN virus causing cases of encephalitis and meningoencephalitis during periods of potential transmission. Appropriate screening of blood donors in Europe, including the exclusion of travellers returning from infected areas, would avoid the risks of transmission of WN virus and other arboviruses. The mechanisms of WN virus (re)introduction in Europe and the cycle of maintenance in infected areas remain to be elucidated. Further studies should focus on the competence of potential mosquito vectors, the possible role of ectoparasites, the persistence of the virus in susceptible hosts, and the genetic susceptibility of hosts to WN infection.

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