FACTORS RESPONSIBLE FOR THE HIGH FREQUENCY OF WEST NILE NEUROINVASIVE DISEASE IN RECENT URBAN OUTBREAKS

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A computerized search of the Medline database from January 1997 to August 2006 for all human West Nile Virus (WNV) outbreaks in European countries and United States was performed using specific key words. Also unpublished aspects present in ArboNet reports were reviewed (www.cdc.gov/WestNile). Three European and five North American urban outbreaks were identified. Detailed clinical descriptions were available for many of these outbreaks. The predominance of WN neurological disease (WNND) was reflected in hospital based surveillance reports. Analysis of surveillance data from WNV urban outbreaks suggests a direct correlation between the number of target susceptible population and frequency of WNND. We explain the higher rate of WNND in the context of urban epidemics by amplification of WNV in human-mosquito-human cycle without previous amplification in a sylvatic cycle by the ornithophilic mosquitoes. WNV can be inter-human transmitted by mosquito vectors (*Culex pipiens*). At each homologous host passage virus acquires an increased human tropism which favours a higher viremic titer and neurovirulence.

Key words: West Nile Virus; WN neurological disease; Urban outbreaks.

INTRODUCTION

WNV is an arbovirus (genus Flavivirus, family Flaviviridae) transmitted to humans by mosquito bite. In the summer of 1996, South-Eastern Romania and especially Bucharest experienced an unprecedented epidemic of West Nile encephalitis/meningitis, with at least 393 hospitalized cases and 17 deaths.[1] Contributing factors included a susceptible avian population and urban/suburban infrastructural conditions that favoured the production of large numbers of mosquitoes (sp. *Culex pipiens pipiens*).[2] At the time, the Romanian outbreak was unique being the first urban epidemic in a temperate geographic area where WNV infections had not occurred before. Moreover, virus transmissions in rural area and outskirts have been moderate suggesting the absence of a regional sylvatic cycle that could generate urban spreading. On the contrary, the new viral introduction was considered plausible and the predominance of neurological cases was interpreted as portentous to a more virulent WNV strain.[3] Subsequent genetic analysis indicated that the strain of West Nile virus responsible for this outbreak was similar to strains that were circulating in northern Africa years before and was nearly identical to a strain that caused outbreaks of encephalitis in Israel in 1998.[4] Slight genetic variations in the virus itself during recent outbreaks might have conferred virulence factors contributing to higher morbidity and mortality than observed during earlier outbreaks.

In most cases (80%), human WNV infection remains asymptomatic, although sporadically relatively mild, influenza like disease with full recovery was described. Infrequently, acute aseptic meningitis or encephalitis occurred. No large outbreak of WN virus fever was reported in Europe until August and September 1996, when more than

500 clinical cases were observed in Romania (Bucharest region), with high rates of neurological disorders and death (up to 10%).[5] WN virus had never been detected in the Western Hemisphere until August 1999, when an outbreak of human WN encephalitis in New York City (56 confirmed cases, 7 deaths) coincided with unusual deaths in crows and exotic birds.[6] The severity of West Nile neuroinvasive disease (WNND) was again observed during this American urban outbreak. We don't have an accepted explanation for the differences in clinical manifestations of infection between urban epidemic pattern and rural sporadic occurrence.

The introduction and subsequent spread of West Nile virus in United States and Canada highlight the critical importance of early diagnostic for the response to any unexpected occurrence of disease and for the management of patients with WNND. The virus area is confined to two basic types of cycles and ecosystems: rural (sylvatic) and urban cycle.[7] The rural cycle is linked to wild, wetland birds and ornithophilic mosquitoes and the human cases were rare. The urban cycle is no so limited attracting synanthropic or domestic birds and mosquitoes (mainly *Cx. pipiens/molestus)* feeding on both, birds and some mammalian species: humans, dogs, cats, horses, etc. Dangerous central nervous system complications (encephalitis and meningo-encephalitis) were rare in typical rural environment but urban outbreaks were characterized by severe neurological disease that affected primarily older adults. This review highlights recent research into WNV epidemiology, including recent advances in understanding of the host-virus interaction at the ecological levels.

METHODS

A computerized search of the Medline database from January 1997 to August 2006 for all zoonotic or human WNV outbreaks in European countries and United States was performed using specific key words: WNV outbreaks, encephalitis, acute aseptic meningitis, WN virus fever, vectors (mosquitoes) and amplifying hosts (birds).

The following indication for considering WNV infection diagnosis and requesting a specific virological investigation were obtained from European Technical Guidance Document.[8]

WNV fever: fever over 38 ^{o}C and at least one of the following: myalgia, arthralgia, headache, fatigue, photofobia, lymphadenopathy, maculopapular rash; occurring during a period when arboviral transmission is possible or in area where arboviral transmission is possible.

Encephalitis: altered mental state (altered level of consciousness, coma, lethargy, agitation) and/or other evidence of cortical involvement (*e.g.* focal neurological findings, seizures) and cerebrospinal fluid (CSF) pleocytosis with predominant lymphocytes and/or elevated protein and no alternative microbiological cause identified.

Meningitis: headache, stiff neck and/or other meningeal signs and CSF pleocytosis with predominant lymphocytes and/or elevated protein and no alternative microbiological cause identified.

Laboratory diagnosis of these viral infections was based on viral isolation or detection by immunoassay and polymerase chain reaction (PCR).

In United States, the Centers for Disease Control and Prevention collaborated with state and local health departments to establish ArboNet, an electronic surveillance system for tracking West Nile virus infections in humans, mosquitoes, birds, and other animals (www.cdc.gov/WestNile). This system started in 2000. Data from ArboNet have documented the dramatic westward spread of West Nile virus across North America resulting in intense epidemic activity in Louisiana, Illinois, Michigan, and Ohio in 2002; Colorado in 2003; and Arizona and California in 2004. Most of the aspects discussed in this review were based on ArboNet reports.

Because data were derived from a passive surveillance system, our study had at least two major limitations. Passive surveillance data can have an inherent reporting bias towards cases with more severe illness. Therefore, these data may not have reflected the age distribution, symptoms, and severity of disease found in all possibly infected persons. Second, the presence or absence of symptoms and hospitalization dates for cases with incomplete case report forms make uncertain some differences between epidemiologic characteristics of outbreaks in different locations. This may have affected our results, particularly with regard risk factors associated with severity of disease in WNV infection.

RESULTS

Three European and five North American urban outbreaks was identified (Table 1). Detailed clinical descriptions were available for many of these outbreaks. The predominance of neurological cases was reflected in hospital based surveillance reports. The disease was generally more severe, with a higher than normal case-fatality rate in urban environment. The central nervous system was usually involved, and acute aseptic meningitis or encephalitis was frequently described. Fever, rash and conjunctivitis were rarely observed. In all WN virus urban epidemics, clinical features included abrupt onset of disease, asthenia, high fever (up to 39°C–40°C), headache, and vomiting.

Table 1

The distribution of clinical syndromes (percent from total confirmed cases) during recent urban WNV epidemics

Site and year	No confirmed cases	Encephalitis	Meningitis	WNV fever	Reference
Bucharest, 1996	394	66.1	22.7	11.2	1, 2
Volgograd, 1999	826	10.2	56.1	33.7	9
NewYork, 1999	62	63	27	8	6
Israel, 2000	417	57.9	15.9	24.4	10
Hartford (Cn), 2002	310	42.2		55	11
Cleveland (Oh), 2002	316	70.1		27	12
Oakland; Wayne (Mi), 2002	644	87		9	13
Cook County (Il), 2002	884	35.2	23.2	37.4	14

The high proportion of neuroinvasive disease cases among reported cases of West Nile virus disease may reflects surveillance reporting bias. Serious cases are more likely to be reported than mild cases. Also, the passive surveillance system was not designed to detect asymptomatic infections. Data from population-based surveys indicate that among all people who become infected with West Nile virus (including people with asymptomatic infections) less than 1% will develop severe neuroinvasive disease.

Results from serologic surveys show that symptoms develop in approximately 1 in five persons with West Nile virus infections and that neuroinvasive disease occurs in 1 in 140–160. Known these proportions, it would seem that approximately 940,000 persons have been infected with West Nile virus in the United States, and 190,000 of them have become ill, only until 2004 end.[17] The risk of neuroinvasive disease increases with age and appears to be substantially higher among immunodepressed than in the general population. In the interval 1999-2006, ArboNet registered 23975 WNV infections including 9849 WNND cases (41.1%) and 962 deaths (4%). In the referred American outbreaks 2216 cases were confirmed including 1416 WNND (63.9%) and 166 deaths (7.49%). The incidence of WNND varied between 42 and 90% and was directly related to the cities or counties census (Fig. 1).

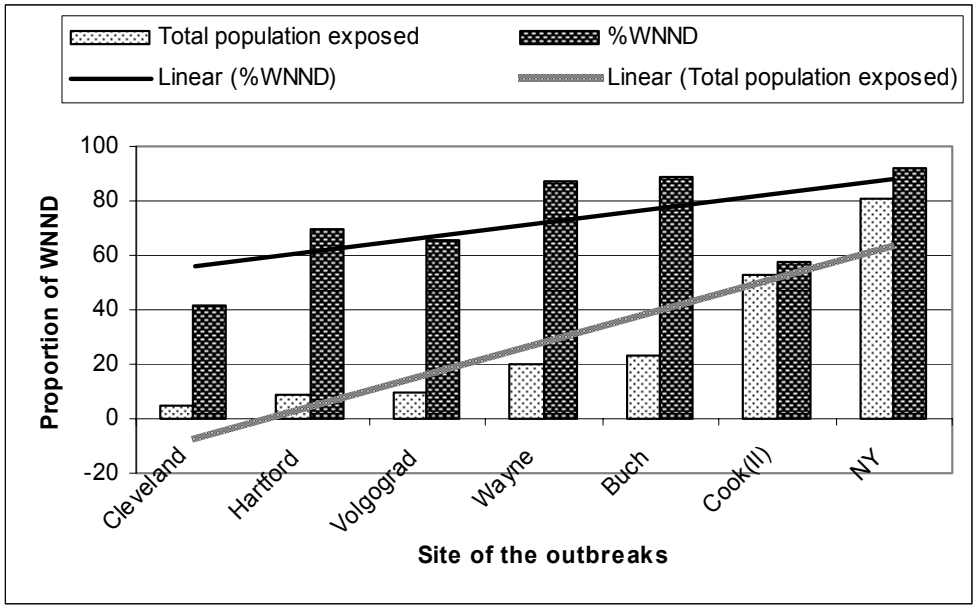

Fig 1. Analysis of surveillance data from WNV urban outbreaks suggests a direct correlation between the number of target susceptible population and frequency of WNND.

In Europe, the frequency of WNND, varied between 66 and 89% and correlated with the population cities numbers. Enhanced surveillance in US may have contributed to this difference.

In all these outbreaks, large urban and suburban populations live in close proximity to mosquito vector breeding sites. The abundant mosquito species harbouring WNV might partially explain the greater magnitude of the recent WNV outbreak than previously seen during the sporadic disease activity. Efforts to quantitatively link human disease with indices of mosquito exposure facilitated a better understanding of ecologic conditions and risk factors for human transmission.

The principal foci of WNV activity were identified as densely populated (>5,000 people/km^2) residential communities in coastal counties. In almost all instances a correlation both temporally and spatially between the isolation of WNV from field-collected mosquitoes and subsequent human cases was observed. In most years the incidence of human cases closely paralleled the number of virus isolations made from mosquitoes with both peaks falling in early September. The isolation of WNV from field-collected mosquitoes is a sensitive indicator of virus activity that is associated with the risk of human infection that habitually extends from early August through the end of October in US and in Romania too.

DISCUSSIONS

West Nile virus is a striking example of an established viral disease that after being transplanted to a new continent has adapted and expanded its dominion in North America. However, we don't know why West Nile disease became endemic in North America but not in Europe, even though the virus and the vector are present on both continents.

The environmental factors that affect how insect-borne viruses spread need to be more investigated in their specific details confined to each location. On the other hand, the risk of neuroinvasive disease due to West Nile virus is not determined only by virus genetic characteristics. The foci of highest incidence are likely to shift with ecologic variations.

Even if WNV rarely cause disease in their maintenance hosts or vectors, viremic blood is available for vector-borne transmission. The favourite mechanisms to explain virus survival in the absence of disease were: vector vertical transmission, vector overwintering, or persistent infection in the arthropod or vertebrate host. For WNV is characteristic amplification cycles in birds (maintenance host) or in vectors. There are two kinds of vector populations: ornitophilic mosquitoes (especially, *Culex pipiens pipiens*) and autogenous mosquitoes (having the ability to develop and lay eggs without taking blood meal). The first one prefers bird blood meals, but autogenous mosquitoes have a strong preference for human blood meal.[2]

In the presence of susceptible hosts, an environment that favours rapid arthropod amplification, an efficient mechanism for dispersal, and a suitable climate, WNV can be interhuman transmitted by mosquito vectors. At each homologous host passage virus acquires an increased tropism which favours a higher viremic titer and neurotropism. That scenario may explain the higher rate of WNND in the context of urban epidemics (Fig. 2).

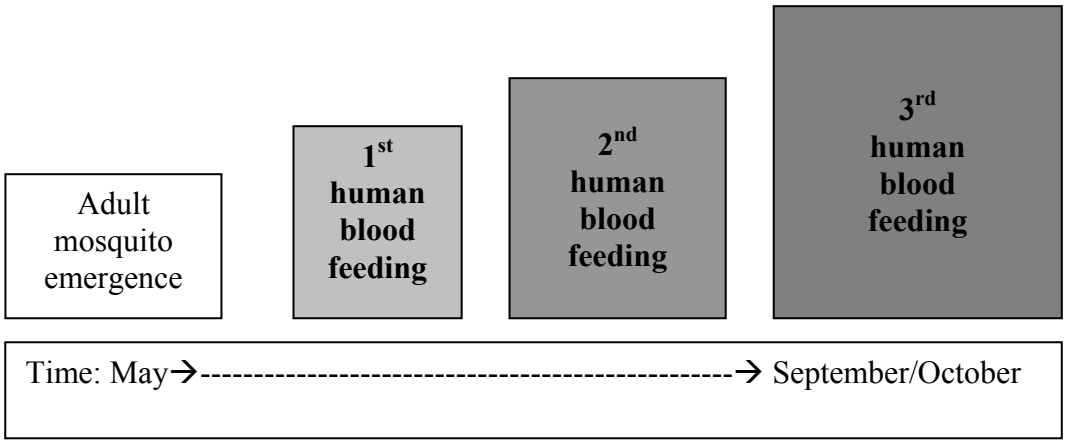

Fig. 2. Relation between mosquito aging and WNV transmission efficiency and neurotropism. The number of blood feedings is unpredictable but is proportional to population density and the environmental exposure. The background of boxes suggests the mosquito amplified viral titer and viral neurotropism.

Once a decision is made to investigate a WNV outbreak, three types of activities are generally involved: the epidemiologic investigation; the epizootical investigation, and the environmental investigation. While these activities often occur simultaneously throughout the study, it is conceptually easier to consider each of them separately.

Epidemiologic investigation. Outbreak investigations have essential components as follows: 1) establish case definition; 2) confirm that cases are "real"; 3) establish the background rate of disease; 4) find cases, decide if there are clusters of cases (outbreaks); 5) examine the descriptive epidemiologic features of the cases; 6) generate hypotheses concerned the source; 7) collect and test samples in order to verify the hypotheses; 8) implement control measures; and 9) interact with the media, inform the public.

The epizootical investigation for WNF consist of four main components: (1) monitoring of vectors (mosquito populations and their infection rate); (2) domestic vertebrate surveys (domestic birds, horses, dogs, cats etc); (3) sentinel birds (domestic ducks rather than chickens), (4) wild vertebrate survey (birds including captive wildlife in zoos, and pet animals)

The environmental investigation is more complex and begins with the monitoring of standing water, simply because many of the mosquito vectors breed in water. West Nile virus is primarily an infection of birds and culicine mosquitoes, with humans and horses serving as incidental hosts. In urban setting, amplification of virus in human–mosquito–human cycle begins when adult mosquitoes emerge in early spring and continue until fall. Among humans, the incidence of disease peaks in late summer and early fall. Birds provide an efficient means of geographic spread of the virus especially in rural environment where birds-mosquito-birds amplification cycle prevails. In most American outbreaks**,** an epizootic disease associated with the death of substantial numbers of birds was occurring in the cities area. An independent investigation of dead birds by veterinarians and wildlife specialists found pathological evidence of multiorgan involvement, including encephalitis, and specimens obtained at necropsy tested positive for WNV infection.[15]

For reasons that are unclear, the spread of West Nile virus into Latin America and the Caribbean has resulted in surprisingly scarce reports of human disease, despite conditions that should favour the transmission of mosquito-borne arboviruses.[16]

Ecological factors that have allowed human exposure to a natural host carrying the virus were involved in the introduction of the infection into humans. This probably occurred in the past in rural area. Zoonotic introductions of this sort may occur on occasion in isolated populations but may well go unnoticed so long as the recipients remain isolated. But with increasing movement from rural areas to cities, such isolation is increasingly rare. After its likely first move from a rural area into a city, WNV spread regionally along highways, then by long distance routes, including air travel, to more distant places. This last step was critical for WNV and facilitated today's regional epidemics. Social changes that allowed the virus to reach a larger population and to be transmitted despite its relatively low natural transmissibility were instrumental in the success of the virus in its newfound human host.

Ecological interactions can be complex, with several factors often working together or in sequence. For example, population movement from rural areas to cities can spread a once-localized infection. The loop of infrastructure in the overcrowded and rapidly growing cities may disrupt or slow public health measures, perhaps allowing establishment of the newly introduced infection. Finally, the city intercontinental links may also provide a gateway for further dissemination of the infection.

In urban environments, rain-filled tires or plastic bottles are often breeding grounds of choice for mosquito vectors. The resulting mosquito population boom is complemented by the high human population density in such situations, increasing the chances of stable transmission cycles between infected and susceptible persons.

It remains to be determined whether the European endemic foci of WN virus are in themselves sources of infection for other birds that migrate across Europe and do not necessarily reach the natural reservoir situated in sub-Saharan Africa. If this is the case it will be necessary to define the strategies for detection of virus overwintering in the European temperate climate.

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