

ORIGINAL ARTICLE

West Nile Virus in the New World: Trends in the Spread and Proliferation of West Nile Virus in the Western Hemisphere

H. Artsob^{1,2}, D. J. Gubler³, D. A. Enria⁴, M. A. Morales⁴, M. Pupo⁵, M. L. Bunning⁶ and J. P. Dudley^{7,8}

¹ National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada

² Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, Canada

³ Asia-Pacific Institute of Tropical Medicine and Infectious Diseases, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

⁴ Instituto Nacional de Enfermedades Virales Humanas, Pergamino, Argentina

⁵ PAHO/WHO Collaborating Center for Viral Diseases Pedro Kouri – Tropical Medicine Institute, Havana, Cuba

⁶ USAF Biomedical Sciences Corps for Public Health HQ AFMOA SOUTH/SG3PN, Kelly, TX, USA

⁷ Science Applications International Corporation, Modeling and Analysis Division, Rockville, MD, USA

⁸ Department of Earth Science – University of Alaska Museum; Institute of Arctic Biology – University of Alaska-Fairbanks, Fairbanks, AK, USA

Impacts

- West Nile Virus (WNV) continues to spread in the Western Hemisphere, with new range extensions reported from southern South America.
- The record numbers of human WNV infections recorded in Canada during 2007, up to more than 50% over previous record set in 2003, demonstrate that the public health impacts of WNV in North America could increase rather than decrease in future.
- Increased capacity for surveillance and diagnosis is needed to better understand the public health risks and impacts from WNV in South America, Central America and the Caribbean Basin region.

Keywords:

West Nile Virus; Western Hemisphere; epidemiology; surveillance; public health; trends

Correspondence:

Harvey Artsob. National Microbiology Laboratory, Public Health Agency of Canada, 1015 Arlington Street, Winnipeg, MB, Canada R3E 3R2. Tel.: 1 204 789 2134; Fax: 1 204 789 2082; E-Mail: harvey_artsob@phac-aspc.gc.ca

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Summary

The observed patterns and variations in the ecology, epidemiology, distribution and prevalence of the West Nile Virus (WNV) in different areas of the Western Hemisphere make this pathogen of particular importance as a model for understanding the potential risk factors associated with emerging pathogens worldwide, particularly those involving zoonotic pathogens whose epidemiology involves the potential for vertical transmission in arthropod vector species, and horizontal and vertical transmission within and among vertebrate host species. Record numbers of human WNV cases were recorded in Canada during 2007, with >50% more cases than documented in any previous year. Although overall numbers of human infections recorded in the United States were not exceptionally high during 2007 relative to epidemic levels reported in 2002 and 2003, the state of Oklahoma reported that the highest-ever number of human WNV cases and the numbers of human cases recorded in Canada were 50% higher than previous record levels recorded in 2003. The record and near-record numbers of human WNV infections recorded in several regions of North America during 2007 have important implications for the future management and surveillance of WNV vectors and reservoirs in North America. The spatiotemporal distribution of WNV infections in humans and animals recorded during 2007 in North America and South America have important implications for the surveillance and management of public health threats from WNV in the Western Hemisphere. Serological surveys conducted in areas of intense WNV transmission in the United States have reported low prevalence of antibodies to WNV in human populations, indicating that additional epidemic outbreaks of human disease from WNV can be expected in the future.

Introduction

West Nile Virus (WNV) is an emerging pathogen whose ecology and epidemiology span the multidimensional interface between viral pathogen, invasive arthropod disease vectors, wildlife, domestic animals and human beings. WNV is a mosquito-transmitted virus of the Japanese encephalitis virus (JEV) serogroup viruses of the family Flaviviridae that is closely related to St. Louis encephalitis virus (SLE) (Americas and the Caribbean), JEV (eastern and southern Asia) and Murray Valley encephalitis virus (Australia). WNV was first identified and described from a human case of febrile illness in Uganda in 1937. Since 1937, however, WNV has expanded its range to tropical and temperate areas of Africa and Eurasia, including the Middle East, central Asia, southern and eastern Europe, Russia, India, Indonesia, and – since 1999 – across most of the temperate and tropical regions of the Western Hemisphere, including most of North America, Central America and the Caribbean, and substantial areas in northern and southern South America (Fig. 1).

West Nile Virus was not regarded as a significant human pathogen for a long time because most human infections identified had been associated with asymptomatic infections or mild febrile illness (Hayes, 1989). However, as stated by Gubler (2007), a virus subtype with greater epidemic potential and virulence emerged in the early 1990s. Since 1999, WNV infections involving severe or fatal disease have been documented in a broad range of vertebrate taxa, including birds, humans and numerous

other species of mammals, reptiles and anurans. The observed dynamics and expanding distribution and prevalence of WNV in the Western Hemisphere make this particular pathogen of great importance as a model for understanding the potential risk factors associated with emerging pathogens worldwide. The extremely broad host and vector range of WNV makes this pathogen extremely difficult to control or eradicate, and WNV has now become established in continental and island ecosystems in the Western Hemisphere between latitudes 50°N to 40°S.

West Nile Virus belongs to the JEV serogroup, the members of which share similar lifecycle and ecological characteristics. Birds serve as the natural vertebrate host and mosquitoes of the genus *Culex* as the principal enzootic and/or epizootic vectors. Severe or fatal disease often occurs in humans and mammals which serve as incidental, and usually dead-end hosts. Horizontal transmission of WNV has been demonstrated for some species of birds, including blue jays (*Cyanocitta cristata*), black-billed magpies (*Pica pica*), ring-bill gulls (*Larus delawarensis*), American crows (*Corvus brachyrhynchos*) and domestic geese (*Anser anser*). WNV infections acquired through consumption of infected tissues have been reported for birds, mammals and reptiles (Glazer, 2004). Phylogenetic studies have identified two main lineages of WNV. Strains from Lineage I are present in Africa, India, Australia and the Western Hemisphere, and have been responsible for recent epidemics in Europe, the Mediterranean basin, the Americas, and strains from Lineage II have been reported only in sub-Saharan Africa and have not been associated with epidemic transmission (Beasley et al., 2004).

The spread of WNV in both the Old and New World appears to be the result of the emergence of a WNV strain with greater epidemic potential and virulence in birds, humans and horses in northern Africa during 1994 (Marfin and Gubler, 2001; Gubler, 2007). Between 1994 and 1999, this new WNV strain dispersed rapidly across the Mediterranean Basin region and into the Middle East, and southern and eastern Europe. Between 1996 and 2000, WNV outbreaks involving severe and fatal neurological disease in humans or equines were documented in Africa, the Middle East, Europe and North America (Zeller and Schuffenecker, 2004). A particularly virulent WNV Lineage I strain that was identified from dying migrating storks and domestic geese in Israel during 1998 caused fatal infections of humans in Israel and the United States during 1999 (Giladi et al., 2001; Lanciotti et al., 2002). A number of bird species that have high WNV loads do not develop severe or fatal disease and are likely capable of migrating while infected (Rappole et al., 2000). Recent experimental infection of migratory birds has shown that WNV infection does not inhibit migratory

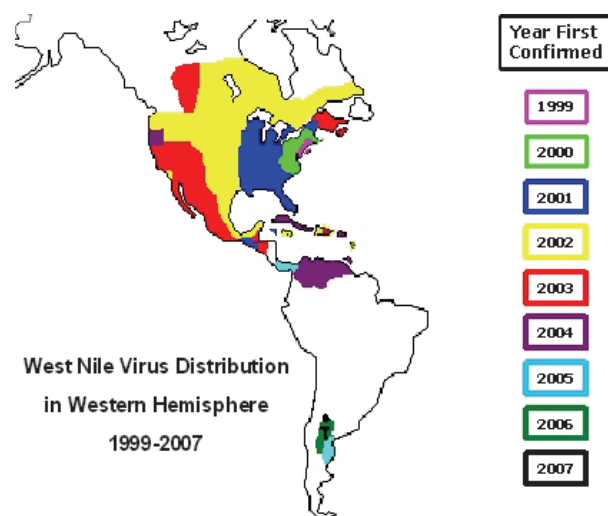


Fig. 1. Dispersal of West Nile virus in the Western Hemisphere 1999–2007.

behaviour, and that migratory status does not affect WNV titres in infected birds (Owen et al., 2006). Studies have also demonstrated WNV infection of storks that migrated from Africa to Israel (Malkinson et al., 2002).

West Nile Virus is vertically transmitted within some species of *Culex* and *Aedes* mosquitoes. Overwintering female *Culex* mosquitoes can potentially serve as perennial reservoirs for this virus in temperate and tropical ecosystems. WNV has been detected in at least 61 species of North American mosquitoes, although not all these species are likely to be competent vectors (Glazer, 2004; Gubler, 2007). Mosquitoes of the genus *Culex* are the most important vectors of WNV in North America. Most species of *Culex* tested to date have been identified as potentially efficient enzootic or amplifying vectors for WNV. Vertical transmission has been experimentally confirmed in *Culex pipiens* (Dohm et al., 2002), and major outbreaks of WNV in Eurasia and the Americas involving severe neurological disease were associated with *Cx. pipiens*, a species that had not been recognized previously as an important vector for WNV (Hayes, 1989). Mosquito species experimentally confirmed as competent vectors for WNV transmission include *Aedes vexans*, *Culex erythrothorax*, *Culex nigripalpus*, *Culex pipiens pipiens*, *Culex pipiens quinquefasciatus*, *Culex restuans*, *Culex salinarius*, *Culex stigmatosoma*, *Culex tarsalis*, *Culiseta inornata*, *Ochlerotatus dorsalis*, *Ochlerotatus melanomon* and *Ochlerotatus sierrensis* (Sardelis et al., 2001; Goddard et al., 2003; Turell et al., 2002). Vertical transmission of WNV has been documented for *Cx. pipiens*, *Culex tritaeniorhynchus*, *Aedes albopictus* and *Aedes aegypti* (Baqar et al., 1993; Dohm et al., 2002). There appears to be a higher risk of human neuroinvasive disease from WNV in areas where the primary WNV vectors are *Cx. tarsalis* and *Cx. quinquefasciatus* mosquitoes (Lindsey et al., 2008).

Predominant mosquito vectors for WNV vary according to geographic location and local ecology. *Culex pipiens* is an important enzootic/epizootic vector of WNV in urbanized areas throughout its range in Asia, Africa and the Americas. *Culex tarsalis* has been identified as the most important vector of WNV in most areas of central and western North America (Reisen et al., 2004; Kilpatrick et al., 2006). In the central Great Plains region of North America, mosquito species that transmit WNV include *Cx. tarsalis*, *Cx. pipiens*, *Cx. restuans*, *Cx. salinarius* and *Culex erraticus* (Gujral et al., 2007). In Florida and coastal areas along the Gulf of Mexico, potential vectors include *Cx. quinquefasciatus*, *Cx. nigripalpus*, *Cu. melanura*, *Cx. salinarius*, *Oc. condolezens* and *Oc. taeniorhynchus* (Blackmore et al., 2003; Hribar et al., 2004; Glazer, 2004). *Culex tarsalis* and *Cx. quinquefasciatus* have been identified as principal vectors in southern California (Reisen et al., 2004). *Culex nigripalpus*, *Culex bahamensis* and *Cx. quinquefasciatus* appear to be important

vectors for WNV in Central America and the Caribbean (Lefrançois et al., 2006; Barrera et al., 2008).

The distribution and population dynamics of *Cx. tarsalis* are believed to be the key determinants in the intense epizootic transmission of WNV in the western United States and Canada during 2007. *Culex tarsalis* distribution in Canada extends through the southern central portions of the three prairie provinces where record numbers of human cases were recorded during 2007 (Manitoba, Saskatchewan, Alberta), and *Cx. tarsalis* is believed to have had a major role in facilitating the explosive spread and proliferation of WNV in North America during 2003 (Kilpatrick et al., 2006).

Human Disease and Clinical Presentations

The spectrum of human clinical disease from JE serogroup viruses is quite broad, ranging from asymptomatic infections and mild febrile illness to severe and fatal neurological disease (meningitis, encephalitis) (Hayes and Gubler, 2006). Although WNV was historically considered to be among the least virulent of the JE serogroup viruses, recent WNV epidemics associated with severe and fatal disease in birds, humans, horses and a broad spectrum of other vertebrate taxa have been reported from Eurasia and North America during past decade. The discovery of novel mechanisms of virus infection and transmission (i.e. ingestion of tissues from infected animals, organ transplants, blood transfusions, intrauterine transmission) has forced a re-evaluation of the public health importance of WNV virus (Zeller and Schuffenecker, 2004). Studies of recent WNV epidemics indicate that about 80% of human infections were asymptomatic, while approximately 20% presented with a sometimes severe but self-limited dengue-like viral fever syndrome (West Nile Fever).

West Nile Virus infection exhibits similar epidemiologies in tropical and temperate regions of the Old World, in which <1% of documented human infections are associated with neuroinvasive disease including encephalitis, meningitis, polyradiculoneuritis and polio-like flaccid paralysis (Lindsey et al., 2008). Case-fatality rates (CFRs) among confirmed WNV cases have ranged from 4% to 15%. Acute clinical symptoms are typically resolved within a period of 7–10 days in most cases, but patients with neuro-invasive disease who survive, frequently exhibit sustained or permanent neurological sequelae. Other clinical presentations reported in association with WNV infections include Guillain-Barré syndrome, chorioretinitis, myocarditis, nephritis, pancreatitis, hepatitis and a fatal haemorrhagic syndrome (Paddock et al., 2006). Although neurological disease presentations are believed to occur in <1% of WNV infections, organ transplant

patients who acquire WNV infections have an estimated 40-fold greater risk for developing severe neurological disease presentations than members of the general population (Kumar et al., 2004; CDC 2007). WNV has shown an increasing tendency for neuroinvasive disease over the past decade, involving meningitis, encephalitis and acute flaccid paralysis.

Of interest is the puzzling fact that, to date, there have been only rare documented instances of severe and fatal neurological disease associated with WNV infection from humans and equines in South America and the Caribbean archipelago. At least part of this phenomenon may be attributable to limited surveillance and diagnostic capacity; however, the presence of a number of other enzootic and endemic flaviviruses whose clinical presentations may be confused with WNV and whose antibody may be partially protective, may be down-regulating clinical illness and viruses (Gubler, 2007). Other epidemiological factors are believed to be involved as well. The low frequency of severe disease associated with WNV in tropical America is not unexpected, because JE, SLE and WNV exhibit a similar epidemiology: epidemics associated with severe neuroinvasive disease occur mostly in the temperate regions of their geographic distribution, although transmission in general occurs widely in tropical countries of Asia and the Americas (Monath, 1980; Solomon and Vaughn, 2002). This phenomenon may be attributable in part to higher species diversity and lower population densities associated with bird communities in the tropics: the diversity of avian species in tropical regions includes many species that are poor amplifying hosts of WNV; hence mosquitoes feeding on these species are less likely to get infected. This reduces the likelihood of a large build up of virus among mosquito and bird populations, driving a corresponding decrease in the likelihood of a large number of human cases (Artsob et al., 2006).

A second hypothesis to explain why more humans and equines do not develop severe neurological disease in tropical areas of their distribution involves cross-reactive flavivirus antibody. There are numerous endemic and/or enzootic flaviviruses in the Caribbean and Central and South America, including dengue, SLE, yellow fever, Ilheus, Roccio, Cacipacore, Aroa, Naranjal, Bussuguara and Iguape viruses (Sabattini et al., 1998; Gubler, 2007). A number of these viruses are members of the JE serogroup. Although there is no known cross-protective immunity among flaviviruses, there is experimental evidence that heterotypic flavivirus antibody can modulate or down-regulate clinical illness and reduce virus loads. Thus, it is possible that the widespread flavivirus antibody among human, domestic animal and bird populations in tropical America down-regulates or modulates clinical illness and

viraemia associated with WNV infection and, thus, reduces transmission.

A third explanation is that intrinsic or extrinsic factors associated with hosts and the environment may be involved in selecting genetic variants of the virus that are less virulent. Heterotypic flavivirus antibody could influence this selection, as could innate immunity that has evolved as a result of frequent exposure to numerous flaviviruses (Gubler, 2007).

It is likely that at least some WNV infections are not detected, or are misdiagnosed as dengue virus infections, given that surveillance for dengue infection in tropical American countries is typically based on results of the IgM capture ELISA, which is a non-specific test for flavivirus IgM antibody (Gubler, 2007). Cross-reaction with different flavivirus antigens depends on the infecting virus, and after primary infections with dengue viruses, antibody-positive reactions often occur with antigens from WNV, SLE virus, JEV and yellow fever virus (Gubler and Sather, 1988). In primary infections with these latter viruses, however, the antibody reaction is fairly specific, with only limited cross-reaction with dengue and other flavivirus antigens. On the other hand, in secondary infections with all of the mosquito-borne flaviviruses tested, there is an extensive cross-reactivity regardless of the infecting virus (Gubler and Sather, 1988; Gubler, 2007). Thus, many human WNV infections, especially those in persons who have had a previous heterotypic flavivirus infection, will yield positive results with the dengue IgM ELISA and will be erroneously diagnosed as dengue infections rather than WNV infections. In light of these and other important differential diagnosis issues, the enhancement of laboratory and field diagnostic, epidemiological and vector-control capabilities in WNV-enzootic countries worldwide is critical to the development of effective prevention and control strategies for control and response capabilities for WNV and a growing number of other emerging and re-emerging zoonotic and vector-borne diseases (Gubler, 2007).

Dispersal and Proliferation in the Americas and Caribbean

Although the means by which WNV was introduced to the Americas may never be determined, possible mechanisms for introduction include:

- 1 Infected birds imported through the international exotic animal trade to the United States from Israel or nearby areas of the Middle East.
- 2 Infected mosquitoes or mosquito larvae imported accidentally from Israel or nearby areas of the Middle East via air or surface shipping networks inside cargo

containers, agricultural products, vehicles, or manufactured goods.

- 3 Infected humans travelling between Israel and the United States during the summer of 1999, at the time of an WNV epidemic in Tel Aviv (Giladi et al., 2001; Gubler, 2007). The low level of viraemia in humans makes this introduction possibility less attractive to many but does have its advocates.

The geographic range of WNV has expanded dramatically during the 8 years subsequent to its first identification in the Western Hemisphere, expanding from an epicentre in New York City westward and southward across the United States as far north as the boreal forest region of central Canada, and southward to the Argentine pampas and the central Chilean coastal plain (Fig. 1). Following its emergence in New York City during the summer of 1999, local spread occurred in the greater New York City metropolitan area and southeastern New York state, Connecticut, New Jersey and Maryland, where a single infected dead bird was recovered in the city of Baltimore. By the end of 2000, WNV had dispersed over a large area of the Atlantic coastal plain and piedmont areas of eastern New England southward as far as North Carolina. A second major hotspot emerged during 2001 along the central Gulf of Mexico coastal area of Florida and southeastern Georgia, along with an increased prevalence in previously reported areas of the Atlantic Coastal region of the United States. By the end of 2001, WNV had spread from the Atlantic and Gulf coastal regions westward across the southern and central Mississippi Valley region, northward into the Ohio Valley and the central and eastern Great Lakes region of the United States and Canada, and southward into Central America and the Caribbean (Chiapas, Mexico: Ulloa et al., 2003; El Salvador: Cruz et al. 2005). An autochthonous human WNV case with neuroinvasive disease presentations was confirmed in the Cayman Islands during 2001 (Campbell et al., 2002), and birds collected in Jamaica in early 2002 tested positive for WNV neutralizing antibodies suggesting that WNV reached the western Caribbean through southward migrating birds during the winter of 2001–2002 (Komar and Clark, 2006). WNV is believed to have been a contributing factor in an episode of widespread equine mortality observed in El Salvador during the period between November 2001 and March 2002 (Cruz et al. 2005) as well as southern Mexico and the western Caribbean (Dupuis et al., 2003; Ulloa et al., 2003; Komar et al., 2005; Lefrançois et al., 2006).

West Nile Virus proliferated and dispersed explosively across most of North America during 2002, achieving a nearly continuous distribution across the most of continental North America by December 2002 when WNV-infected birds were confirmed from most areas of the

continental United States and Canada east of the Rocky Mountains, cordillera, as well as Idaho, southern California, and the Puget Sound area of Washington. WNV was well established in southern Mexico and the Caribbean by the summer of 2002, when WNV activity was reported in birds and/or equines in Mexico (Estada-Franco et al., 2003) and the Caribbean islands of Jamaica, Hispaniola and Guadeloupe (Eastern Antilles) (Dupuis et al., 2003; Komar et al., 2005; Lefrançois et al., 2006). During 2002, an isolated but apparently autochthonous human WNV case was documented in Los Angeles, CA from a resident of a neighbourhood located near the Los Angeles Internal Airport (CDC 2002), although there was no contemporaneous evidence of WNV in ongoing bird and mosquitoes surveillance programmes in southern California (Reisen et al., 2004). WNV was first detected in California and southern Arizona through bird and mosquito surveillance programmes during July 2003, and available evidence suggests that introduction to this region occurred through northward migration of migratory birds infected in Mexico, where WNV had been in widespread circulation since July 2002, rather than westward dispersal of birds from the southern Great Plains or Gulf of Mexico region across the major ecological barriers of the Sonoran and Mojave Desert region, and Sierra Nevada mountain range (Estada-Franco et al., 2003; Reisen et al., 2004).

During 2003, WNV activity was detected in an extensive area of Central America including 22 additional states in Mexico, and from Belize and Guatemala. In the Caribbean, evidence for WNV activity was detected in Cuba, Puerto Rico, and the Bahamas during 2003 and WNV antibodies were demonstrated in birds or equines from northern Colombia, eastern Venezuela and Trinidad during 2004. The first confirmed WNV human cases were documented in Cuba during 2003 (Pupo et al., 2006), with continuing zoonotic transmission recorded in 2005, and 2006 (Table 1). The first recorded human WNV infections on the island of Hispaniola were documented in Haiti during September 2004 (Beatty et al., 2007). A purported human WNV case in Uruguay during 2004 may have been contracted by an individual while visiting the United States (ProMED-mail 2004); other countries that have reported detecting WNV infections in travellers returning from the United States include Canada, the Czech Republic, Denmark, France, Germany and the Netherlands (Hubálek et al., 2006).

The first known autochthonous human cases of WNV infection on the South American mainland occurred during 2005 in Colombia, while WNV infection in equines and birds was first recorded in Argentina in 2005, followed by the first known human WNV encephalitis cases in 2006 with additional human cases recorded in 2007 (Morales et al., 2006; Diaz et al., 2008). Surveillance for

Table 1. Human symptomatic infections in the Western Hemisphere due to West Nile Virus 1999–2007

State province	1999	2000	2001	2002	2003	2004	2005	2006	2007 as of 8 January 2008
United States									
Alabama	–	–	2	49	37	16	10	8	24
Georgia	–	–	6	44	50	21	20	8	49
Minnesota	–	–	–	48	148	34	45	65	101
Oklahoma	–	–	–	21	79	22	31	48	101
Wyoming	–	–	–	2	375	10	12	65	181
Montana	–	–	–	2	222	6	25	34	201
North Dakota	–	–	–	17	617	20	86	137	369
Colorado	–	–	–	14	2947	291	106	345	555
New York	62	14	15	82	71	10	38	24	21
Canada									
Ontario	1*	–	–	394	89	14	101	42	16
Quebec	–	–	–	20	17	3	5	1	2
Saskatchewan	–	–	–	–	947	5	61	20	1436
Alberta	–	–	–	–	143	3	58	51	584
Manitoba	–	–	–	–	275	1	10	40	323
Cuba									
Santi Spiritus	–	–	–	–	2	–	4	4	No data
Villa Clara	–	–	–	–	1	–	–	–	No data
Matanzas	–	–	–	–	–	–	–	1	No data
Uncertain	–	–	–	–	–	–	–	2	No data
Argentina									
Entre Ríos	–	–	–	–	–	–	–	1	–
Chaco	–	–	–	–	–	–	–	3	1
Córdoba	–	–	–	–	–	–	–	1	1
Santa Fe	–	–	–	–	–	–	–	–	2
Formosa	–	–	–	–	–	–	–	–	1

*Fatal case involving person returning to Canada from visit in New York City. Additional non-autochthonous cases have been reported from provinces of British Columbia, Nova Scotia, New Brunswick, Prince Edward Island and the Yukon.

WNV was initiated in South America following the discovery of the virus in North America, in anticipation of the possible dispersal of the virus to South America through migratory birds, infected humans or animals, or commercial trade networks. In Argentina and other countries, WNV surveillance activities have been established within ongoing surveillance programmes for dengue and SLE viruses (Avilés et al., 2001, Spinsanti et al., 2008). Evidence of WNV on the South American mainland was first discovered in equines, and unlike the situation in North America there have been relatively few records of WNV in birds reported to date.

Evidence of the circulation of WNV in equines was first detected in northern South America (Colombia, Venezuela) during 2004 (Mattar et al., 2005; Bosch et al., 2007). Serological evidences of WNV circulation was found in horses from Santa Fe, Buenos Aires, Corrientes and Cordoba provinces in 2005, and WNV was isolated from dead horses and birds in northern and central Argentina during 2006 (Morales et al., 2006). WNV has been detected in relatively few species of birds in South America to date, compared to the number of resident

and exotic birds species with WNV infections recorded in North America and the Caribbean (>300 species: Gubler, 2007). Studies in Venezuela identified evidence of WNV infections in two species of passerines (*Turdus leucomelas*, *Coereba flaveola*) and a domestic chicken (*Gallus gallus*) (Bosch et al., 2007); WNV-infected *Coereba flaveola* have also been reported from the Caribbean islands (Dupuis et al., 2005). Surveys conducted in Argentina have detected antibodies to WNV were detected in ducks (Anatidae: *Dendrocygna bicolor*) and coots (Rallidae: *Fulica leucoptera*) (Pérez et al. 2008). It is interesting to note that species of the passerine genus *Turdus* with apparent WNV infections have been reported from the Caribbean and mainland South America, given that the congener species *Turdus migratorius* has been identified as a highly competent amplifying reservoir and important migratory bird vector for WNV in North America (Komar et al., 2003; Kilpatrick et al., 2006).

The broad vertebrate host and vector range of WNV coupled with a capability for vertical transmission in mosquito vectors and horizontal transmission in some vertebrate host species may have been key factors in the

successful spread of epidemic/epizootic WNV. As of 2007, WNV had been isolated from 61 species of mosquitoes and infection demonstrated in >1300 species of birds, and >130 species of non-avian vertebrates (Gubler, 2007). Non-avian vertebrates infected include rodents, bats, canines, felines, ungulates and reptiles, in addition to equines and humans. Many mammal species appear to be susceptible to WNV infections, and fatal WNV encephalitis has been documented in mammals of numerous disparate taxonomic lineages (rodents, primates, ungulates, carnivores, lagomorphs, chiropterans) including species such as cow, horse, dog, cat, sheep, rabbit, raccoon, squirrels, striped skunk, bats, llama, alpaca, Rocky Mountain goat, harbour seal, black bear, whitetail deer, reindeer, Barbary macaque and Indian rhinoceros ('among others: USGS, 2007'). Reptiles that can become infected by WNV include American alligator, Nile crocodile, monitor lizard and green iguana (Steinman et al., 2003). Potential anuran hosts include at least two species of frogs, bullfrog (*Rana catesbeiana*) and lake frog (*Rana ridibunda*). Experimental studies have implicated American alligators as an efficient amplifying host for WNV, and a possible factor in the proliferation of WNV in the Gulf Coast region of southeastern North America. Infected alligators develop viraemia levels that can sustain WNV transmission to mosquitoes, and which are of much longer duration than those observed in birds (>2 weeks in alligators versus maximum 7 days in birds: Klenk et al., 2004).

Many species of migratory birds in North America are known to be highly susceptible to WNV, and the spread and proliferation of WNV in North America appears to be associated with long-distance dispersal through infected birds. High rates of morbidity and mortality are often associated with passerine bird species, especially corvids (crows, jays, magpies, ravens, grackles, etc.), although fatal WNV infections have also been reported among birds of highly disparate taxa, including raptors (owls, hawks), flamingos, parrots, gulls and geese. The observed timing and pacing of the spread of WNV appears consistent with initial local dispersal from the New York City metropolitan area into nearby areas of the mid-Atlantic region of eastern North America during 1999–2000 mediated by American crows (*Corvus brachyrhynchos*), and subsequent dispersal southeast into Florida and the Gulf Coast region by migrating passerines (e.g. blue jay *Cristata cristata*, American robin *Turdus migratorius*, common grackle *Quiscalus quiscula*), and subsequent redistribution and proliferation northward and westward by other migrant and non-migrant passerine species infected on both wintering and summering grounds since that time.

Although other studies have identified American robin *Turdus migratorius* as the a principal reservoir for WNV

transmission in North America (Kilpatrick et al., 2006), experimental studies and indirect evidence suggest that the common grackle (*Q. quiscula*), a highly gregarious and mobile migratory species whose migratory range includes most of North America east of the Rocky Mountains and south of Hudson Bay (50°N latitude), may have been a principal agent for the explosive dispersal and epidemic proliferation of WNV across North America during 2002. There is a marked positive correspondence between the recorded range and breeding population densities of common grackles with the recorded geographic distributions of human and equine WNV cases during 2002, with the geographic distribution of human WNV cases clustered within areas documented as having high breeding densities of *Q. quiscula*, with few or no cases of WNV in equines reported from areas where common grackle breeding densities are either low or non-existent during 2002 (Fig. 2) (Smith, 2006; USGS, 2008). Experimental studies have identified that the common grackle is a highly competent avian reservoir for WNV, with the second highest reservoir index ranking found among 25 bird species tested, with a higher resistance to WNV mortality among infected individuals than observed in most other passerine species tested (Komar et al., 2003). Despite their higher documented resistance to mortality from WNV, dead bird surveys conducted on US military installations documented WNV-positive grackles from at least 12 US states within the breeding range of this species during 2002 and 2003 (MA, MD, NY, GA, FL, OK, NE, KS, TX, IL, WV, KY: Dudley, 2003).

In 2002 and 2003, WNV virus caused the most extensive epidemic of arboviral meningoencephalitis ever documented in the history of the United States (Hayes and Gubler, 2006). There was also a large epizootic of WNV encephalitis in equines in 2002, with 14 571 cases reported and a CFR approaching 30% (Gubler, 2007). The number of equine cases decreased dramatically in subsequent years, however, due to intensive equine vaccination campaign. In 2002, the epicentres of human transmission were situated in the Mississippi Valley and Ohio Valley region of the central United States, and in the Mississippi Delta region of Louisiana – a distribution paralleling that seen in an epizootic of SLE during 1975 (Monath, 1980). There were 4156 cases reported in the United States during 2002, with 2946 cases of neuroinvasive disease and 284 known deaths (10%) (Hayes and Gubler, 2006). In Canada, the virus occurred in the southern portion of five provinces along the northern border of the United States, with 414 human cases reported primarily from Ontario, but with cases also reported from Quebec (Lessard, 2007), mirroring the human cases hotspot distribution in the contiguous Ohio Valley region of the USA. In 2003, the number of recorded cases more than

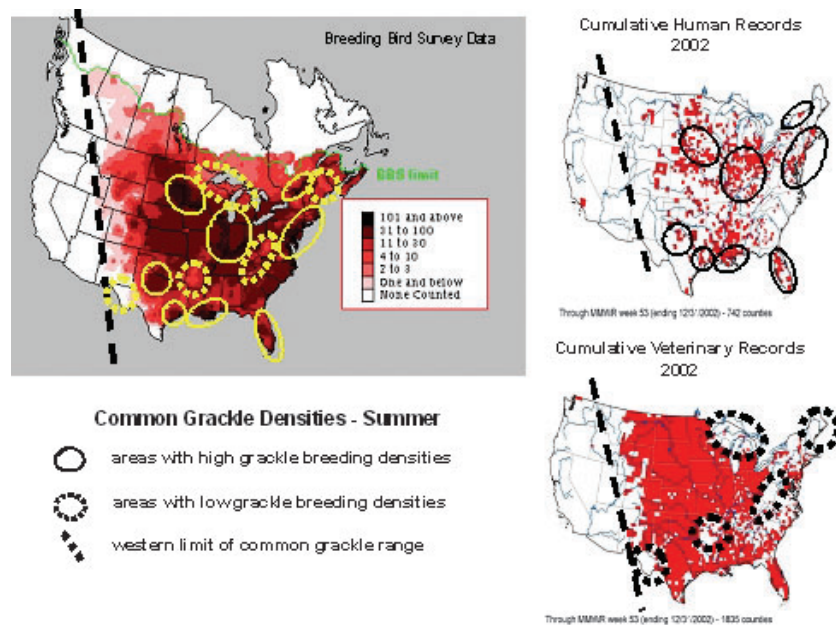


Fig. 2. Grackle migratory patterns and 2002 West Nile Virus distribution.

doubled and the epicentre of transmission shifted west to the central plains states and Canadian prairie provinces. There were 9862 cases recorded in the United States for 2003, with 2866 cases of neuroinvasive disease and 264 fatalities, with a 9% CFR among persons with neuroinvasive disease. In Canada, the virus was reported during 2003 in seven of eight provinces that border the United States including Manitoba, Saskatchewan, Alberta, Ontario, Quebec, New Brunswick and Nova Scotia. A total of 1481 human cases were reported in Canada for 2003, of which 1351 were from the prairie provinces including 142 from Manitoba, 937 from Saskatchewan and 272 from Alberta (Lessard, 2007).

In 2004, zoonotic transmission waned somewhat, with 2539 cases, including 1142 cases of neuroinvasive disease, and 100 deaths (9%), reported in the United States (Hayes and Gubler, 2006) and only 25 cases reported in Canada (Drebot and Artsob, 2006). The epicentre of transmission was in California and in the intermountain states. During 2005, 3000 cases were reported; there were 1294 cases of neuroinvasive disease and 119 deaths (9%); in 2006, the number of reported cases increased to 4269, with 1455 cases of neuroinvasive disease and 194 deaths (12%) in the United States (Hayes and Gubler, 2006; Gubler, 2007). In Canada, 225 and 151 cases were reported in 2005 and 2006 respectively (Drebot and Artsob, 2006; Lessard, 2007). The number of documented human cases in Canada reached unprecedented and unanticipated levels during 2007, with a total of nearly 2400 confirmed human WNV infections (Public Health Agency of Canada 2007).

Status and Trends During 2007

During 2007, there was an explosive epidemic of WNV among humans in the central Great Plains bioregion of North America paralleling and in some areas surpassing that recorded during the first wave of mass human transmission during 2003, with record numbers of cases in the Canadian provinces of Saskatchewan, Manitoba and Alberta, and exceptionally high numbers of cases in the adjacent US states of Montana, North Dakota, Minnesota, Wyoming, Colorado and Oklahoma (Table 1). As of 30 November 2007, a total of 2381 WNV cases were reported in Canada including 1436 from Saskatchewan, 584 from Manitoba and 323 from Alberta (Public Health Agency of Canada 2007). Of particular interest is the observation that the ratio of United States to Canadian cases was much different than previous years, with a ratio of only 1.5 American cases identified to every Canadian case recorded during 2007 while ratios in past years have ranged from a previous low of about 7 : 1 for 2003 to a high of nearly 100 : 1 for 2004 (Table 2). Unusually high numbers of cases (100% greater than annual median/mean values for prior 3-year period 2004–2006) were also recorded from the eastern Gulf Coastal Plain bioregion of southeastern United States (Alabama, Georgia) (Fig. 3).

Exceptionally heavy rains, including some record rainfall events, were recorded during the spring and summer months within some areas of the northern Plains regions of the United States and Canada that experienced unusually high levels of WNV cases during 2007 (Minnesota,

Table 2. Comparative numbers and ratios of reported human WNV infections in the United States and Canada (1999–2007)

Year	USA*	Canada†	Human case ratios USA/Canada
1999	62	1‡	62 : 1
2000	21	0	–
2001	66	0	–
2002	4156	414	10 : 1
2003	9862	1495	6.6 : 1
2004	2539	26	98 : 1
2005	3000	238	13 : 1
2006	4269	154	28 : 1
2007	3510	2381	1.5 : 1

*Figures from CDC website as of 8 January 2008.

†Figures from Public Health Agency of Canada as of 24 November 2007, includes all reported symptomatic and asymptomatic cases.

‡Travel-associated case in patient who had visited New York City (Nash et al. 2001).

Saskatchewan, Alberta). Although most of the continental United States experienced below-average rainfall levels, many areas of the central Plains region experienced the episodes of unusually heavy rainfall during the spring and summer (May–July) that would have been highly favourable for mosquito populations. Exceptionally, high levels of mosquito breeding habitat availability coupled with exceptionally hot summer and unusually warm fall temperatures provided exceptionally good recruitment and prolonged activity for mosquito populations in the prairie regions of the United States and Canada (Lessard, 2007). An overview of Canadian WNV trends by region appears

to indicate minimal risk for human WNV infections in Atlantic Canada, where occasional WNV positive birds have been identified in Nova Scotia and New Brunswick but no locally contracted human cases have been identified. Ontario and Quebec have experienced repeated episodes of WNV activity during the past several years but relatively limited numbers of human cases since 2002 (Table 1). The Canadian prairie provinces of Saskatchewan, Manitoba and Alberta have produced the greatest numbers of human cases to date, while British Columbia has not experienced any locally acquired WNV cases to date. British Columbia has populations of mosquito species known to be important WNV vectors, including *Cx. tarsalis*, but the extent to which *Culex*-driven epizootics will pose a risk in British Columbia has yet to be determined. Short day length, which drives *Culex* mosquitoes into diapause, with relatively cool daytime temperatures during the late summer and fall may be significant limiting factors for the efficient local transmission of WNV to human populations, and these microclimatic factors may be responsible for limiting mosquito transmission of WNV in the Atlantic coastal provinces of Canada and the state of Maine, and the cool temperate rainforest areas in British Columbia, Washington State and Oregon.

Only limited surveillance data from Central America, South America and the Caribbean region were available in 2007. Surveillance programmes in Argentina detected cases in humans and equines during 2007, with cases documented in four provinces (Table 1). The first confirmed human WNV infections detected in Puerto Rico during 2007 were identified in three persons whose blood donations tested positive for WNV by nucleic acid-amplification test (NAT) screening (Torres Aponte et al., 2008).

Areas in United States and Canada reporting elevated levels of human WNV cases during 2007

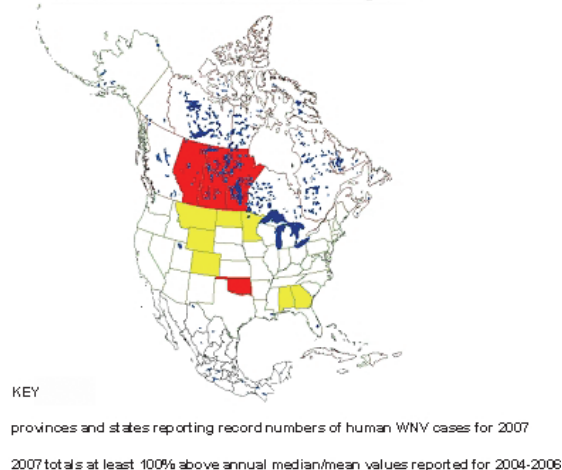


Fig. 3. Areas in United States and Canada reporting elevated levels of human WNV cases during 2007.

Conclusions

West Nile Virus is now enzootic throughout much of the Western Hemisphere, and there is little chance that WNV will be eliminated from most areas of its current range. The broad host and vector range of WNV, and the capability of this virus for vertical transmission in mosquitoes and horizontal transmission in birds and mammals ensure that this pathogen will continue to persist and proliferate within the Americas for the foreseeable future. Although surveillance for WNV and other arboviruses has improved greatly in the United States and Canada during the time since this virus was first introduced to North America, unfortunately, the patterns of human infection observed during 2007 demonstrate that we still do not have the ability to accurately anticipate and predict when and where WNV epidemics/epizootics will occur.

Surveillance for WNV in tropical and subtropical areas of Central and South America is complicated by the

presence of a number of other enzootic/endemic flaviviruses, especially SLE and dengue virus, and by the difficulty of accurately diagnosing and distinguishing between human infections with these and closely related viruses (Gubler, 2007). Moreover, mosquito-control programmes lack adequate personnel, equipment and tools in most of the region. The accurate and timely detection and the diagnosis of WNV infections of humans in tropical and subtropical regions of the Americas are complicated by the variability of clinical presentations of different flaviviruses, including the existence of neurological and hepatic injury in dengue and dengue haemorrhagic fever, WNV and SLE. Although there are ongoing surveillance programmes for dengue and SLE in many countries, most suspected human WNV cases in Central America and the Caribbean cannot be clinically evaluated or verified due to a lack of laboratory diagnostic capacity among countries in this region.

Surveillance programmes must also take into account the possibility of the introduction of other similar diseases, such as chikungunya virus, an arbovirus that can exhibit similar presentations in humans and which like dengue virus is transmitted by *Ae. aegypti*, a globally distributed invasive mosquito species that is widely established in tropical and temperate latitudes of the Americas and the Caribbean Basin. Chikungunya has expanded its range in recent years, was recently introduced to Italy and the island of Mauritius through infected humans, and may now have become permanently established in southern Europe and Mauritius (Palma-da Cunha-Matta et al., 2004; Soares et al., 2006; Paddock et al., 2006; Mondini et al., 2007; Pialoux et al., 2007; Beltrame et al., 2007; Charrel et al., 2008). The recent history of dengue and chikungunya viruses reinforces the need for entomological and virological surveillance in all areas where these viruses occur.

Natural disasters, particularly meteorological events such as cyclones, hurricanes, and flooding, usually affect vector-breeding sites and vector-borne disease transmission adversely. The development of El Niño (warm ocean current off the South American coast) may also have important implications for the global public health. Global warming is also a confounding factor that must be taken into account with regard to the potential establishment and spread of vector-borne diseases (Anyamba et al., 2006). Recent experience with the spread and establishment of WNV in the Western Hemisphere, and chikungunya and bluetongue viruses in Europe, should be seen as yet another wake-up call regarding the potential for the emergence of arthropod-borne diseases as potentially serious emerging public health threats in the industrialized temperate latitude regions of North America and western Europe.

In conclusion, WNV transmission will be very difficult to prevent and control because of the poor public health infrastructure to deal with vector-borne and zoonotic diseases. The cost-effectiveness of human vaccines for WNV is uncertain. There are a number of vaccines being developed for WNV infection, some of which are already being effectively used to prevent equine infection (Gardner et al., 2007; MacLachlan et al., 2008). A major dilemma for human use, however, is to identify the target population, such that vaccination will be cost-effective (Monath, 2001; Zohrabian et al., 2006). Currently, vaccination would have to target persons aged >50 years in all areas of the United States and Canada, there is a risk for recurrent epizootic/epidemic transmission. Improvement of the laboratory diagnostic, epidemiological and vector-control infrastructure will be critical for the development of effective prevention and control strategies for WNV infection, as well as for other potential emerging vector-borne viral diseases, such as urban yellow fever and Rift Valley fever, which given globalization and current climatic trends, may have the potential to spread rapidly into temperate latitudes of North America and Europe.

The enhancement of laboratory diagnostic, epidemiological and vector-control capacity in WNV-enzootic countries worldwide is critical to the development of effective prevention and control strategies for control and response capabilities for WNV and a growing number of other emerging and re-emerging zoonotic and vector-borne diseases. Health authorities in Latin America and the Caribbean should be prepared and sustain surveillance systems for vector-borne diseases and zoonoses to detect and manage outbreaks of these diseases in human and animal populations.

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