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Commentary

Resurgence of West Nile neurologic disease in the United States in 2012: What happened? What needs to be done?

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ABSTRACT

The resurgence in cases of neurologic disease caused by West Nile virus (WNV) in the United States in 2012 came as a surprise to the general public and to many non-arbovirus researchers. Following the introduction of WNV into the US in 1999, the number of human infections rose dramatically, peaking in 2002–03. However, cases declined from 2008–11, and it was unclear if the virus would continue to have a low-level endemic transmission pattern with occasional outbreaks, like the related flavivirus, Saint Louis encephalitis virus, or a more active pattern with annual outbreaks, including occasional years with large epidemics, like Japanese encephalitis virus. The large epidemic in 2012 suggests that the United States can expect periodic outbreaks of West Nile fever and neurologic disease in the coming years. In this paper, we consider the causes of the upsurge in WNV infections during the past year and their implications for future research and disease control measures.

Following the introduction of West Nile virus (WNV) into the United States in 1999, the number of human cases of WN fever and neurologic disease rose dramatically, peaking in 2002–3. However, cases declined from 2008–11, and it was unclear if the virus would continue to have a low-level endemic transmission pattern with occasional outbreaks, like the related flavivirus, Saint Louis encephalitis virus (SLEV), or a more active pattern with annual outbreaks, including occasional years with large epidemics, like Japanese encephalitis virus (JEV). The resurgence in cases of WNV neurologic disease in 2012 therefore came as a surprise to the American public and to many non-arbovirus researchers. The size of the 2012 outbreak suggests that the US can expect periodic epidemics of WN fever and neurologic disease in the coming years. In this paper, we consider the causes of the upsurge in WNV infections during the past year and their implications for future research and disease control measures.

1. Background: West Nile virus

WNV is a mosquito-borne RNA virus in the genus *Flavivirus*, family *Flaviviridae*, that is maintained in nature in a basic transmission cycle involving wild birds and *Culex spp.* mosquitoes. For many years following its first isolation in Uganda in 1937, WNV was considered a relatively unimportant member of the flavivirus family. It was known to exist in Africa, southern Europe, the Middle East and Central Asia, where it caused sporadic cases of febrile disease and occasional outbreaks of encephalitis in elderly people and in equines. In 1999, WNV was detected in New York City and surrounding areas, where it caused a large die-off in crows, exotic zoo birds and other bird populations and an outbreak of encephalitis in elderly humans. During the next few years, the virus spread rapidly north, west and south across North America, with the largest epidemics occurring in 2002 and 2003 (Figs. 1 and 2).

WNV has a wide global distribution, and molecular phylogenetic studies have identified multiple lineages or genotypes (Fig. 3). Strains associated with outbreaks of neurological disease in the US clustered together as a subgroup of genotype/lineage 1, suggesting that this subgroup had evolved a more virulent phenotype (Lanciotti et al., 1999). However, later studies in mice demonstrated that strains from lineage 2, the other major genotype, were also capable of causing neuroinvasive disease (Beasley et al., 2002). In the past few years, epidemics in Europe and individual cases of disease in humans and horses in South Africa have been associated with strains from both lineages (Papa et al., 2010; Venter and Swanepoel, 2010), verifying the earlier experimental observations in mice.

WNV is found in all regions of the continental US as well as in southern Canada, Mexico, the Caribbean, and parts of Central and South America. Molecular phylogenetic studies suggest that all isolates are derived from the virus originally introduced into New York City (e.g. May et al., 2011; Osorio et al., 2012; Pesko and Ebel, 2012). The exact manner in which WNV was first introduced is

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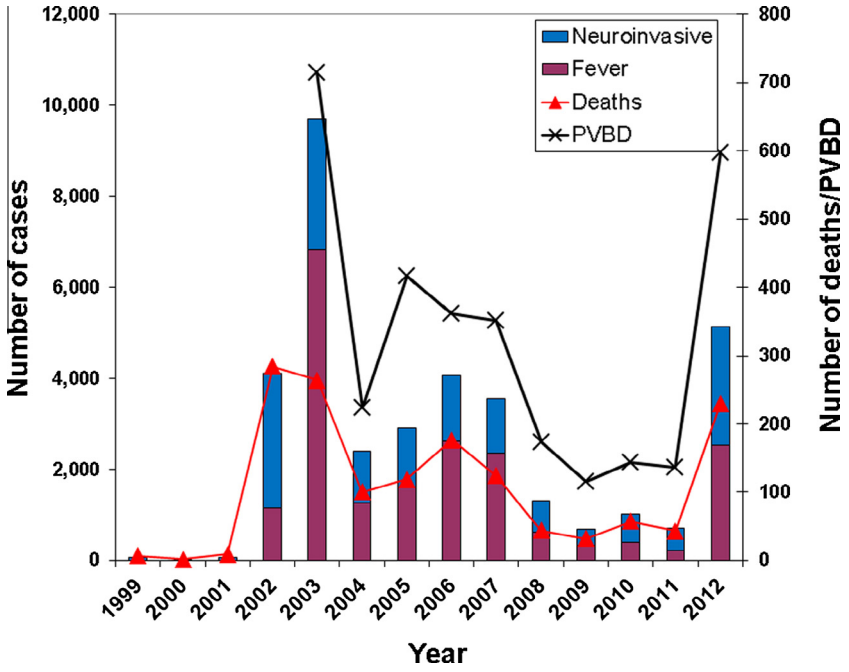

Fig. 1. Numbers of West Nile fever and neuroinvasive disease cases, deaths and presumptive viremic blood donors (PVBD) reported to the US. Centers for Disease Control and Prevention during each year since the introduction of WNV into the US in 1999. (Data from <http://www.cdc.gov/westnile>.)

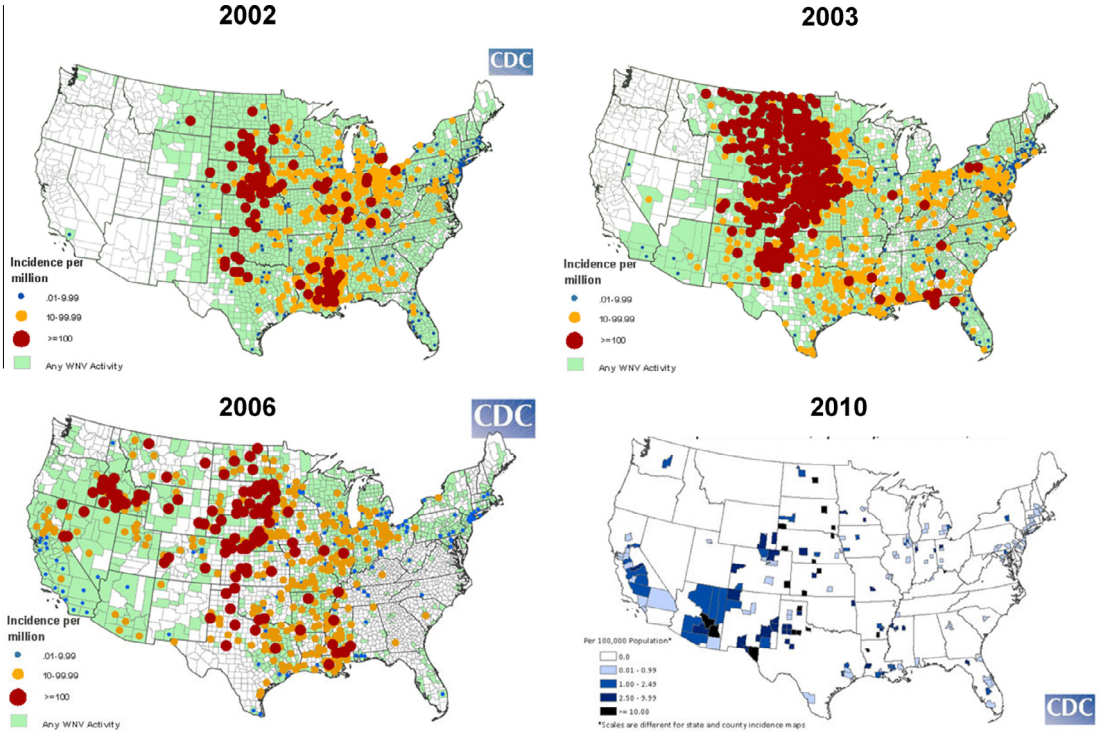

Fig. 2. The varying incidence of West Nile neuroinvasive disease cases by county reported to CDC in selected years, since the peak outbreak years of 2002–03. Note the emergence of individual foci of intense transmission in individual years, such as in Louisiana in 2002, Idaho in 2006 and Arizona in 2010.

unknown, but the most likely scenarios are through the migration or smuggling of an infected bird, or by an infected mosquito "hitching a ride" in an airplane or container cargo coming from the Mediterranean region or North Africa. Regardless, WNV is now firmly established (endemic) in the US. Virus activity is seen mainly during summer, but it may vary, depending on latitude and seasonal temperatures. The largest annual numbers of human neuroinvasive disease cases and deaths were reported in 2002, with 2946 neuroinvasive cases and 284 deaths, with similar numbers in 2003 (Fig. 1). From 2004–7, cases of neuroinvasive disease and deaths declined to about half of the 2002–3 peak years, then declined further during 2008–11, reaching a nadir of 373 neuroinvasive cases

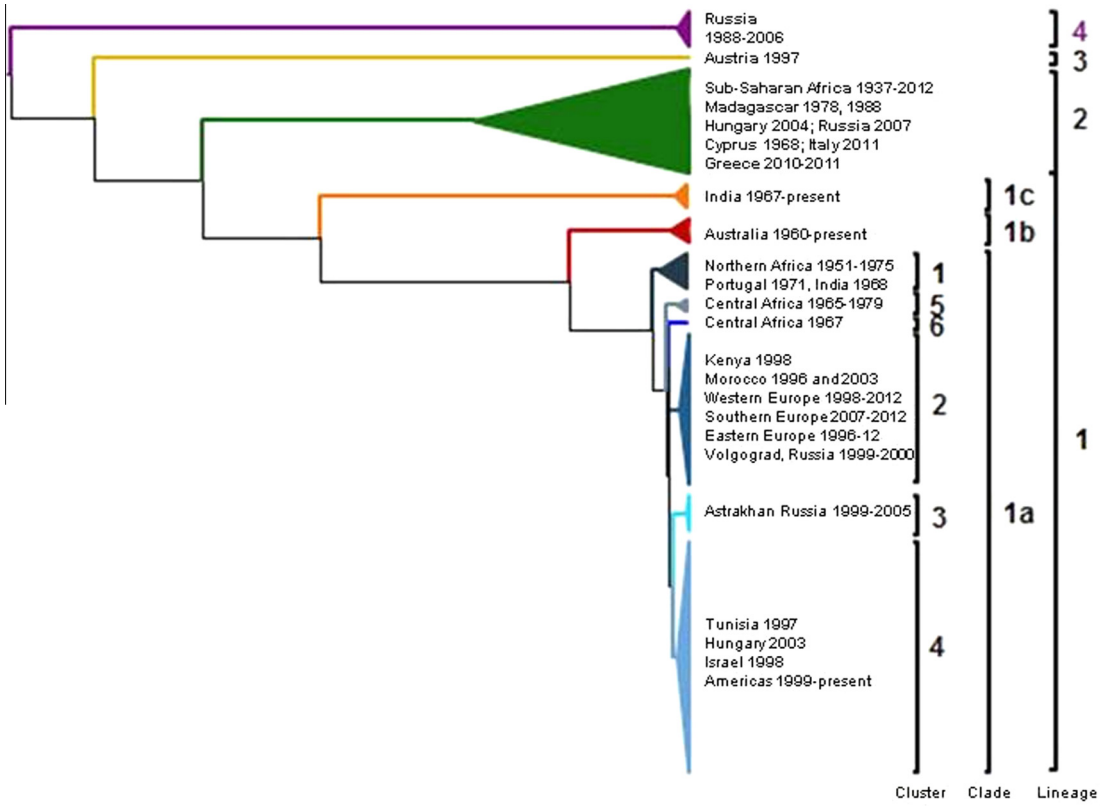

Fig. 3. A neighbor-joining phylogenetic tree, using simplified branches, showing the multiple lineages of West Nile virus. Lineages 1 and 2 are the most geographically dispersed, and include strains associated with outbreaks of neurologic disease in humans, horses and birds in the Americas, Europe, Africa and the Middle East. Strains circulating in the Americas belong to cluster 4 of lineage 1a, as defined by May et al. (2011).

and 32 deaths in 2009. Although case numbers have varied from year to year, evidence exists for virus transmission and disease in humans or animals in essentially all of the lower 48 states every year since 2003.

2. What happened in 2012?

As of December 11, 2012, a total of 5387 human WNV infections have been reported to the Centers for Disease Control and Prevention (CDC), with cases reported from all of the lower 48 states plus the District of Columbia (http://www.cdc.gov/westnile) (Fig. 4). This total includes 2734 cases of neuroinvasive disease, resulting in 243 deaths, placing 2012 on a par with the peak North American epidemic years of 2002–3. Significantly, the case fatality rate for neuroinvasive disease was comparable to that reported previously (approximately 1 in 10), suggesting that the 2012 outbreak was not associated with major changes in the virulence of WNV for humans. Due to delays in case reporting, total numbers will not be finalized until spring of 2013, so these may yet increase slightly.

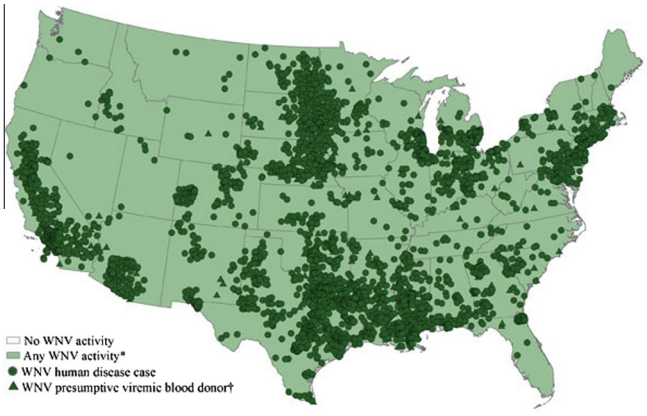

Fig. 4. The distribution of human WNV disease cases in 2012. (Obtained from <http://www.cdc.gov/westnile>).

The impact of the 2012 outbreak was most dramatic in Texas, which accounted for almost one-third of cases of neuroinvasive disease and death. On August 1, the CDC announced the highest number of cases reported since 2004, and more than than 80% had occurred in Texas, Mississippi and Oklahoma (CDC, 2012b). By the end of August, responses in the Dallas-Fort Worth area, the hardest hit by the outbreak in Texas, included aerial and ground spraying of mosquito adulticides, and numerous public announcements regarding the risk of exposure via mosquito bite (CDC, 2012a; TDSHS, 2012).

Like other arboviral encephalitides endemic in the Americas, such as SLE and eastern equine encephalitis, human cases of West Nile fever and neuroinvasive disease are sporadic in occurrence and focal in their geographic distribution. Transmission now appears to be greatest in the south, west and midwest of the U.S., with Texas and California each reporting the largest number of cases in multiple years since 2004, consistent with their relatively large populations. However, many cases and/or high rates of neuroinvasive disease have been reported in other years from Louisiana, Arizona, Colorado, Illinois, Idaho, North and South Dakota, New York and other states (Fig. 2). The locations where large outbreaks occur have also varied from year to year, demonstrating their focal nature. For example, in 2002, WNV infections in Texas were seen primarily in the Houston metropolitan area, but in 2012 the epidemic was focused in the Dallas-Fort Worth region.

No one fully understands why these arboviral encephalitides are so sporadic and geographically focal in their occurrence, but some probable predisposing factors are warm winters, hot summers and variations in rainfall, all of which impact the density of vector mosquito populations and may also affect reservoir avian hosts, as well as herd immunity among the local wild birds and even the human population. Given that mosquito exposure is the major risk factor for human WNV infection, waning public awareness and complacency following years of declining case numbers may also have contributed to the severity of the 2012 outbreak. However, it is likely that absent or ineffective virus surveillance and vector control measures play a more significant role in allowing explosive transmission events to begin.

Many people have tried to explain or predict sporadic outbreaks for a number of different arboviruses, suggesting that they are caused by factors such as global warming, urbanization, drought, or excessive winter or spring rains. Any or all of these environmental factors may play a role, but the factors that combine to produce ''perfect storms,'' with intense transmission of an endemic virus, are in truth likely to be extremely complex, and are still not well understood. Even though WNV has been present in the US for more than 13 years, more research, data collection and time are still required before epidemiologists and public health officials will be able to accurately predict when and where large outbreaks will occur. Without the ability to predict specific outbreak events, continuing surveillance to detect virus transmission is necessary, and must be linked to effective responses. Molecular studies are currently under way to determine if the WNV strains associated with the recent outbreak in Dallas and other areas differ significantly from those isolated in previous years. However, the severity of the 2012 outbreak most probably resulted from the confluence of multiple factors, including climate conditions, an abundance of mosquito vectors, the availability of many susceptible avian hosts and reduced concern about the risk of infection.

3. What to do next

Because zoonotic diseases involving wild animals and biting insects are essentially impossible to eradicate, WNV is here to stay. Given the focal nature of outbreaks, it is currently impossible to predict precisely where WNV activity will occur each year and the number of human cases. This variability means that it will be difficult to plan for epidemics at the federal, state and local levels, and to justify the continued costs of surveillance during periods of low virus activity, particularly when financial resources are limited. It is therefore essential to prioritize how limited funds will be utilized, and to coordinate efforts between the various levels of government and public health agencies. Large outbreaks of WNV will occur again, and the only question is when and where.

When cases of human WNV infection decreased after 2003, so did funding for surveillance and research. As the 2012 epidemic demonstrated, there is a clear need for continued study of the epidemiology of WNV, including surveillance across the country to help public health officials improve planning for future outbreaks and respond quickly to developing epidemics. Environmental control of *Culex* mosquitoes is also important, since it will result in the reduction in virus transmission and human disease. Although insecticides and larvicides play an important role in vector control, their rational use requires appropriate resources and ongoing surveillance, and this costs money.

Accurate and rapid diagnostic tests for WNV infection are also important. They are currently available in the form of molecular methods to detect viral nucleic acids in acute patient samples and blood donations and serologic assays to detect early antibody responses. Because of the antigenic cross-reactivity between WNV and other flaviviruses such as SLEV, yellow fever and dengue viruses, confirmatory testing using neutralization assays is still required in many cases. The effective and timely utilization of these rapid assays, which can be performed in clinical laboratory settings, is critical in identifying and responding to presumptive events of intense virus transmission.

Because the number of asymptomatic, viremic blood donors parallels the incidence of human WNV disease (Fig. 1), the incidence of positive blood donations may also be a surveillance indicator for virus transmission, particularly in large urban settings. In addition to virus detection and serological diagnostics, there is also a need to isolate viruses from human, mosquito and bird surveillance samples, to facilitate investigations of virus evolution by characterizing functional phenotypes, such as virulence in laboratory animals and infectivity/transmission characteristics in mosquitoes.

The advanced development of antiviral drugs and vaccines against WNV has proved challenging, because of the difficulty of performing human clinical trials to evaluate their efficacy. Such trials require testing before and during ongoing outbreaks, to demonstrate a reduction in the number of human cases. In the US, cases of WNV neurologic disease usually occur during the period from June–September. However, because one cannot specifically predict when and where large numbers of infections will occur in any given year, and it takes time to confirm a sufficient number of cases to undertake an efficacy study, it has been difficult to obtain rapid Institutional Review Board approval from multiple health providers before WNV activity ceases with the end of summer.

The challenge of carrying out clinical efficacy trials was recently highlighted by the termination of a Phase 2 study to assess the candidate therapeutic monoclonal antibody, MGAWN1, which only managed to enroll 13 of a planned 120 subjects during 2009–10 (Clinicaltrials.gov, 2012). The best alternative route to evaluate candidate vaccines and antivirals may be the so-called ''Animal Rule'', based on studies in laboratory animal models that recapitulate human disease. However, the licensure of drugs and vaccines for any infectious disease agent via the Animal Rule has been slow, due to the strict requirements by the Food and Drug Administration that such models adequately represent the human disease and be predictive of the expected outcomes of human treatment or vaccination. Better characterization and validation of animal models of human WNV disease to meet the requirements of the Animal Rule would therefore accelerate the development of antivirals and vaccines.

The flavivirus serogroup of which WNV is a member also contains other significant human pathogens, such as JEV and SLEV. JEV periodically causes large epidemics in many parts of Asia, but even though SLEV is endemic in the Americas, it causes relatively few human cases each year. It is now becoming clear that the epidemiology of WNV in the Americas is more like that of JEV than SLEV. As a consequence, there is much we can learn about the control of WNV from experience with JEV in Asia, including the use of live and killed vaccines that have proved very effective in controlling the latter disease. The World Health Organization and other agencies have established guidelines for JE vaccines that have applicability to the development of WN vaccines.

Many federal and state agencies invested heavily in their research and public health infrastructure when WNV arrived in the US in 1999, but funding for many of these programs was reduced or eliminated after 2005, as the number of human cases decreased. Consequently, many parts of the country were unprepared for the sudden increase in virus activity in 2012, and no antivirals or vaccines were available to treat or prevent the increased number of human cases. WNV is now endemic in North America, and its observed epidemiologic pattern indicates that similar epidemics will occur in the future. Although the precise years and affected regions

cannot be predicted, the season and the disease pattern will be the same. In addition to the morbidity and mortality associated with WNV infection, the average cost of treating each case of neuroinvasive disease costs has been estimated at approximately $30,000 (Barber et al., 2010; Zohrabian et al., 2006), suggesting that the total cost of the 2734 neuroinvasive cases reported in 2012 was >$80M. It therefore seems prudent to reinvest now in research and in the public health infrastructure, to be prepared for the next epidemic.

In a sense, arbovirus epidemics are like floods, hurricanes, or tornadoes: they occur sporadically, but their precise time and location cannot be predicted. However, advanced preparation, continued research to identify and robustly define environmental and other risk factors for large outbreaks, and a well-developed response plan can mitigate the resulting damage and loss of life. For now, this must be our response to the continuing threat of WNV.

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