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1. West Nile virus in the news: what happened in 2012?

2012 was more than just an election year — while much of America was following the political news related to the looming presidential election, a sinister force was making its presence felt across the country.

The summer of 2012 marked the biggest national outbreak of West Nile virus since 2002. In all, 2,873 cases of West Nile neuroinvasive disease, the most severe manifestation of the virus, were reported to the Centers for Disease Control and Prevention (CDC), including 286 deaths. Although cases of West Nile disease were detected in all states in the continental United States, the central United States reported the highest number of West Nile severe disease cases, with Texas shouldering 29% of the disease burden. In fact, what made the Texas outbreak so striking is that just four counties in the Dallas-Fort Worth area accounted for 902 out of 1,868 total reported West Nile cases in the state. Other states hit with large West Nile outbreaks were California, Illinois, Louisiana, and Michigan — together the top five states suffered 56% of the reported national neuroinvasive disease cases.
West Nile virus (WNV) is actually a relative newcomer to the North American continent.

First isolated from a febrile woman in the West Nile district of Uganda in 1937, WNV infections were first detected in the Americas in New York City in 1999. The initial indications of WNV in the United States were cases of encephalitis in humans and horses, and numerous deaths among crows and exotic zoo birds. That year, the virus spread to the neighboring states of New Jersey, Connecticut, and as far as Maryland. By 2002, the virus had made it all the way across the continent, with cases diagnosed in California and heavy activity in the Plains and Rocky Mountain States. During the initial years, health officials wondered whether WNV would establish itself as a permanent feature of the disease landscape, or whether outbreaks would fizzle out and fail to return. However, by 2004, every state in the contiguous United States had reported some West Nile virus activity in either humans or other animals. WNV outbreaks now take place each summer across the nation, but because they occur as scattered or isolated events with varied sizes and locations, they have proven difficult to predict. What we do know is that WNV is firmly established in the United States; indeed, only 117 out of 3,140 counties nationwide have never detected the virus in humans or other animals. The WNV outbreaks in the summer of 2012 helped to definitively answer the question of whether WNV was here to stay: that answer was a resounding “yes.”
3. How did West Nile virus spread across the country so quickly?

The first cases of WNV disease were detected in New York in 1999, but within only four years it had been detected in every state in the contiguous United States. Moreover, WNV had caused substantial outbreaks in widely separated geographic regions. How did the virus get so far so fast?

The answer to this question lies in the complex ecology of West Nile virus. WNV is the causative agent of West Nile fever and West Nile neuroinvasive disease. Like any virus, WNV cannot replicate on its own and requires host cells in which to amplify (see “What does it mean to be a virus”). WNV spread across the country by traveling from mosquito to bird to mosquito to bird, taking advantage of free-ranging birds and mosquitoes, some of which may have been inadvertently assisted by humans along the way. The 11,000 nucleotide WNV genome encodes only 10 proteins (about 100 times smaller than the smallest genome of a free-living bacterium, which encodes 1,354 proteins in 1,308,759 nucleotides of DNA) and because of this limited genetic capacity, it relies on host cells to supply the building blocks used to make and assemble new viruses.

WNV is perfectly suited to life in a mosquito host — it belongs to a family of viruses called the Flaviviridae, many of which are spread by mosquitoes or ticks and are called arthropod-borne viruses or arboviruses for short. The arthropod hosts are called “vectors” because of their role in viral spread. The flaviviruses that are transmitted by arthropods can be divided into two groups: those spread by mosquitoes and those spread by ticks. In addition to causing uncomplicated fevers, mosquito-borne flaviviruses typically are either neurotropic viruses, meaning that they can cause infections of the central nervous system, or are associated with hemorrhagic fevers such as dengue and yellow fever. WNV falls into the first category — it is a neurotropic virus carried predominantly by Culex mosquitoes.

FAQ: WEST NILE VIRUS

What does it mean to be a virus?

Viruses are distinct from all other biological entities on Earth because they lack one key feature of all living organisms: the ability to reproduce on their own.

Like living cells, viruses are comprised of genetic material protected by proteins, and sometimes membranes, but their genomes are vastly smaller than their bacterial counterparts — up to 100s of times smaller! With limited genomic capacity, a virus cannot reproduce on its own. Instead, viruses require a host cell to supply the building materials and machinery needed to make more viruses while the virus provides the genetic blueprint.

Because viruses are completely dependent on their hosts to replicate, they have evolved a vast arsenal of tricks for getting into host cells, co-opting those cells to make more viruses, and then escaping to infect more cells. Viruses have developed these tricks through millions of years of evolutionary battle with their hosts — the host evolves to avoid the virus and the virus evolves countermeasures to evade host defenses and gain access to its cellular machinery. After so much back and forth, most host-virus interactions are very species specific and indeed, many viruses only infect specific kinds of cells within their hosts. Each virus has evolved a life cycle strategy to overcome its inability to reproduce on its own, and that strategy affects when and where disease outbreaks occur.

After figuring out how to invade and replicate in host cells, viruses also have to get from host to host. Some viruses are spread via biting (rabies), sex (HIV), sneezing or coughing (influenza), or fecal contamination of drinking water (polio). WNV uses mosquitoes to carry it from bird to bird, birds being the hosts that it uses for amplification within the environment.
Mosquitoes are called the vectors of WNV, because the mosquito carries the virus to its vertebrate hosts. Once a female mosquito becomes infected by biting an infected animal, she is essentially infected for life. The virus is so well adapted to life in its mosquito host that its infection causes minimal, if any, effects. The female mosquito is able to take blood meals, lay eggs, fly, etc.; because the mosquito remains alive and well, the virus can spread to new hosts.

When WNV is ingested during a blood meal, the virus ends up in the midgut of the mosquito where it attaches to and invades midgut cells. The virus then replicates and spreads to other tissues in the host, a process that typically takes several days but is sped up at higher temperatures. Eventually, WNV makes its way to the mosquito’s salivary glands and salivary secretions. When the infected female mosquito bites a vertebrate animal, she injects some of her saliva to facilitate feeding. Her chemically complex mix of anticoagulants and immune modulating factors also contains the virus, which now gains entry to the new vertebrate host.

Did you know that there are about 160 different species of mosquito in the United States?

WNV has been identified in 65 of them. However, not all mosquitoes are created equal. While many mosquito species can ingest WNV when taking a blood meal from an infected bird host, their different susceptibilities, feeding patterns, and lifestyles mean that they contribute to disease transmission to varied degrees. Mosquito species have strong preferences for which animals they feed upon, as well as day vs. night feeding and indoor vs. outdoor feeding preferences, which influences when they’d likely encounter both infected and susceptible hosts. Mosquitoes such as *Culex pipiens* and *Culex tarsalis* feed on both birds and humans and so are important bridging vectors.
Once a mosquito is infected, it can spread WNV to a number of vertebrate hosts, including humans, birds, horses and other mammals, and even reptiles such as alligators and crocodiles (Figure 1). The most critical hosts in the WNV lifecycle, other than mosquitoes, are certain species of birds. Some species of birds are called amplifying hosts, meaning that when they get infected by a WNV-carrying mosquito, the virus is able to replicate to such high numbers in the blood that a new mosquito coming along for a snack will be able to pick up the virus as well. Remember that Culex mosquitoes are very tiny, and only ingest a few microliters of blood at a time (a drop about 1mm across), so virus levels in the blood need to be pretty high to have a chance of infecting a biting female mosquito (Figure 2).

Not all birds are equally affected. Birds can experience a range of symptoms, from species that show no symptoms to those, like crows and their relatives, for whom the virus is rapidly fatal. The extent to which birds are able to amplify WNV also varies from species to species. Some birds, including common grackles, tufted titmice and crows, can generate the highest levels of virus in the blood currently known for any viral infections. These birds can have up to a billion times more viral particles in their blood than similarly infected humans. Birds maintain these high blood virus levels for 1-5 days, during which time a single “super amplifier” bird can infect 100’s of mosquitoes. While some bird species such as crows experience high mortality, they may still infect mosquitoes before their death.

The immune status of bird populations plays a large role in WNV spread. A bird that survives a WNV infection will be immune for life. Therefore, if the majority of birds in an area have already been infected with WNV and survived, they will not become reinfected upon subsequent encounters with the virus. Without a steady supply of new susceptible amplifying hosts, WNV will not be able to continue to spread efficiently. This phenomenon is called “herd immunity.”
4. How do people get infected with West Nile virus?

Just like birds, humans usually become infected with West Nile virus by being bitten by an infected mosquito. Viruses carried in the mosquito’s saliva enter the blood stream and local tissues where they infect immune cells such as dendritic cells and macrophages.

The virus enters and replicates in these cells, its progeny spreading throughout the body to establish what is known as a systemic infection. However, becoming infected with WNV does not necessarily mean becoming sick. In fact, based on seroprevalence (an indication of infection based on looking for the presence of WNV-specific antibodies in the blood), about 75% of infected humans do not exhibit any symptoms — only a quarter of those infected develop West Nile disease (Figure 3). In reality, compared to other species, humans are rather poor hosts for WNV. For reasons that are not quite clear, WNV does not replicate as well in humans as it does in birds. This means that the amount of virus circulating in our blood (called viremia) remains relatively low, which may be why so few infections produce symptoms. The low concentration of virus in the blood also makes humans poor transmitters of the virus back to biting mosquitoes. Because of the inefficiency with which humans and other mammals, such as dogs and horses, amplify WNV, they are essentially evolutionary dead ends or DEAD END HOSTS. Human-to-human transmission only occurs through rare events like transfer through blood transfusions, organ donation, placental blood supply, or breast milk. Thus humans and horses are simply collateral damage from the WNV point of view.
Most of the people who do become sick during a WNV infection develop what is referred to as “West Nile fever.” After an incubation period of 2 to 15 days, patients experience an onset of symptoms such as fever, headaches, fatigue, muscle pain or aches, nausea, anorexia, vomiting or rash. These symptoms can last for 3 to 6 days. Because the symptoms of West Nile fever look similar to those of a number of other diseases, the only way to diagnose West Nile fever definitively is through laboratory tests, usually detection of a virus-specific antibody, viral proteins, or specific elements of the WNV genome in the blood or other tissues. Because it takes several days for these antibodies to develop, initial tests may be negative; therefore, a doctor will typically diagnose West Nile fever if the symptoms correlate with typical West Nile cases, the patient’s activities make it likely that he or she could have been bitten by an infected mosquito, and West Nile virus has been detected in the area. Repeated tests during the convalescent phase will be positive.

A small percentage of people will develop a much more serious illness called West Nile neuroinvasive disease (WNND). In a rare number of cases (less than 1% of those infected), the virus crosses the blood brain barrier and infects the central nervous system. Virologists and immunologists aren’t sure exactly how this happens. There are several different types of WNND including meningitis (inflammation of the meninges, or membranes covering the brain and spinal cord), encephalitis (inflammation of the brain itself), and acute flaccid paralysis (in which the virus infects the spinal cord, eliciting symptoms that mimic polio). WNND can present as severe headaches, fever, altered mental status, seizures, muscular weakness, and flaccid paralysis. Specifically, the virus infects and kills neurons in certain parts of the brain, and which parts are infected will affect what symptoms are experienced. WNND is fatal in about 10% of cases.

How does our immune system affect disease outcome?

Our immune system battles West Nile virus using three levels of defense. The innate immune system, found in each and every one of our cells, alerts the rest of the immune system to infection by producing signaling proteins called interferons. The interferons activate antiviral proteins to inhibit viral replication and also alert killer T cells to clear the virus. Antibodies produced from B cells are the final line of defense and provide lifelong protection against WNV; once you’ve been infected and survived, you don’t become sick again upon reinfection. However, even though the virus is cleared from the body after antibodies are developed, infected persons can still have consequences from the damage that was done by the virus, particularly if that person had West Nile neuroinvasive disease. It is also possible that neurons were damaged by the immune system itself through the “bystander effect;” to rid the brain of WNV, chemicals called proinflammatory cytokines are secreted by activated immune cells which can damage both infected and nearby uninfected cells.
5. Why do some people get West Nile fever or neuroinvasive disease? Did they become infected with a “bad” virus?

We don’t actually know why the vast majority of people infected with WNV don’t get sick. The initial viral load, or the amount of virus deposited in the bloodstream through the bite of an infected mosquito, may play a role in determining whether or not an individual gets sick. The percentage of people showing no symptoms, or just developing West Nile fever, does not vary greatly among age groups. Genetics may contribute to increased risk; several putative genetic markers of susceptibility have been identified but require additional research to confirm.

We know more about the risk factors associated with WNND. The factors can be grouped into definite, probable, and possible risk factors:

- **Definite** — Your risk of developing WNND greatly increases with age and if your infection is transplant tissue-associated:
  - In fact, the risk of WNND increases roughly 2x for every decade of life.
  - For the younger population, less than 1 in 700 will develop neurological symptoms, but this ratio increases to as much as 1 in 50 in those aged 60 or older.

- **Probable** — Male gender and immunosuppression are probable risk factors.
  - Males and females tend to have about the same infection rate (determined from relative rates of detecting West Nile genome or antibodies in blood bank studies), but males seem to have a slightly higher incidence rate of WNND.
  - Immunosuppression also probably plays a role in determining WNND risk. This puts organ and tissue transplant patients at risk, because they are treated with immunosuppressing drugs.

- **Possible** — Additional possible risk factors include underlying health conditions such as hypertension, diabetes, cancer, renal disease, alcohol abuse, and also a possible genetic basis.
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By far, the biggest determinant of disease outcome in the United States is us, not a “bad virus.” The worldwide WNV “family tree” has two major branches, called lineages, but so far only one of these lineages has been seen in the US. In each of the major lineages, there are isolates associated with mild or severe disease. In general, however, Lineage 1 strains are associated with more severe and neuroinvasive disease. The WNV isolates in the US belong to Lineage 1 and are almost identical genetically, meaning that the virus was probably only introduced to the US once and then spread. The circulating US strain can be viewed as a “bad” relative of the milder Old World strains. While other variants potentially could emerge that further affect its pathogenicity or how well it can cross the blood brain barrier to cause WNND, so far scientists have not seen evidence of this. Remember that WNV is a rather promiscuous virus because it can infect lots of different hosts, from insects to birds to mammals. Generally, viruses like WNV that have a complex life cycle requiring switching back and forth between mosquitoes and other hosts do not change their genetic sequences rapidly. A mutation that helps the virus in one host might limit its replication in another. Therefore, arboviruses like WNV are likely to change more slowly than viruses that infect only one type of host.
Outbreaks occur during the summer months when mosquitoes are abundant and active. Therefore, WNV persistence from year to year depends on the ability of the virus to survive during the winter months, as colder temperatures can kill both mosquitoes and the viruses they carry. Persistence can occur in hibernating female mosquitoes or potentially in vertebrate hosts, as some species of birds and mammals have been shown to sustain persistent infections for several months. Most likely, a small number of infected female mosquitoes survive the winter and can transmit the virus when they emerge from hibernation. These females can also pass on the infection to some of their progeny in the spring. Although only a small proportion of overwintering adults or their progeny may be infected with WNV, only one infected mosquito is needed to kick off a transmission cycle when the right conditions occur. We know that temperature plays a role in the waxing and waning of WNV infections in northern regions — transmission can occur year round in southern states such as Texas and Louisiana where temperature fluctuations between summer and winter are less extreme.

Several factors can influence the size of disease-transmitting mosquito populations during the summer months, with weather patterns playing a dominant role. Mosquitoes rely on warm temperatures to reproduce and develop, so the earlier warm spring temperatures arrive, the greater the potential for early mosquito activity and thus a longer bird-mosquito-bird amplification cycle. Warm temperatures not only increase the rate at which mosquitoes develop from egg to larva to adult, but also increase the rate of viral replication within the mosquito itself and the speed at which the virus reaches the salivary glands. Mosquitoes are also able to digest blood faster in hotter weather and feed more often, thus spreading infections quickly. However, temperature does not tell the entire story.

6. Why was 2012 so bad?

To understand what happened in 2012, you have to know what factors drive WNV outbreaks. For an outbreak to occur, three things are needed: a critical mass of infected mosquitoes, susceptible birds, and humans unprotected from biting mosquitoes. When these three factors converge, an outbreak can happen.
Figure 4: 2012 West Nile virus outbreak

West Nile neuroinvasive disease cases reported to the Centers for Disease Control in 2012

2012 was the United States’ warmest year on record

Data adapted from Centers for Disease Control
The chance of an outbreak also hinges on a fine line between drought and rainfall — for Culex mosquito populations to flourish you need pools of standing water in which they can breed and develop, but not enough rainfall to wash away the developing insects.

Even if infected mosquitoes abound, you still need the right kind of birds around. Remember that bird species also vary in their ability to amplify the virus. A handful of species are “super amplifiers” and their presence combined with infected mosquitoes can launch an outbreak. But even if you have infected mosquitoes combined with the right bird species, the outbreak still might not happen if too many of those birds are immune. If the area contains lots of immune birds from the previous year, the virus won’t find many susceptible hosts in which to amplify. This is why you get cycles of infection every year: outbreaks tend to wane even before the mosquito populations drop because more and more birds become immune. However, birds reproduce annually and the young will be susceptible.

In 2012, the United States experienced a perfect storm of above average temperatures and below average precipitation (Figure 4). Warm weather and near drought made perfect conditions for driving WNV outbreaks, especially when coupled with large numbers of susceptible birds and increased mosquito contact with susceptible humans.

One thing that did not cause the 2012 outbreaks was a change in the virus. Scientists can sequence viral genomes isolated from patients, birds, and captured mosquitoes to look for distinguishing mutations. However, sequencing of WNV isolates did not reveal anything unique about the circulating 2012 strains relative to previous strains. The 2012 WNV outbreak also exhibited a similar mortality rate among people with WNND to previous years, although the overall number of cases was much higher. After years of spread across the continent, the 2012 outbreak very firmly established that WNV is here to stay. Now that the virus is established in the US, it can flare up again when conditions are conducive.
Outbreak severity can be described best in terms of the number of WNND cases; WNND is a reportable disease, so the federal disease surveillance system captures most cases. The extent of an outbreak depends on the environmental factors described above.

We can attempt to model the various factors independently, but predicting how they will intersect is still very difficult. Scientists are getting better at using data from previous years to explain observable trends, but the problem with prediction is that the outbreak cycle depends to some degree on chance. Annually, US scientists observe big differences in numbers of cases between even adjacent counties and really don’t know why. Remember that local outbreaks are driven by weather patterns that are difficult to accurately predict months in advance. The one generalization that experts are willing to make is that we don’t often observe huge outbreaks in the same place in back to back years, which may be because of the buildup of immune birds, and therefore fewer susceptible birds.

In the future, climate change is likely to alter the disease landscape, but what those changes will be are unclear. Clearly global warming might increase WNV prevalence as warm mosquito habitats expand, but precipitation patterns may change as well. Precipitation changes are unpredictable, with some places becoming more arid and therefore more inhospitable to mosquitoes, and others becoming more inundated with rainfall.
8. Can the severity of WNND change from year to year?

Because diagnosis of WNV fever is tricky and thus results in variable reporting from year to year, the ratio of WN fever to WNND is difficult to determine and is often misinterpreted.

Although it appears that in the United States, the ratio of West Nile fever to WNND has remained relatively consistent, it is always possible that a variant could emerge that increases the risk of severe disease. At this point, we can’t predict what that mutation might be or when it might occur. When considering the overall evolution of the virus, the 14 years it has spent in the US is but a blip on the radar. Although the virus hasn’t changed much in terms of the symptoms or percentage of WNND cases it causes, that doesn’t mean that it couldn’t.

West Nile virus mutations

Scientists DO know about a couple of mutations that affect the activity of West Nile virus — a mutation has been identified that makes the virus more virulent in crows, and another mutation occurred in 2002 that allowed the virus to be transmitted more efficiently in two important species of Culex mosquitoes.

It’s important to remember that viruses like HIV and influenza mutate rapidly to evade the human immune system and in response to the drugs we use to treat them. These mutant strains can then spread from human to human. WNV cannot spread directly between people except under special circumstances so any treatments that we use will not increase the chance that a resistant or more virulent strain will emerge. Further, any strain that increases the risk of WNND in humans will also have to be able to replicate efficiently in both mosquitoes and birds. This is unlikely, but not impossible, so scientists are watchful for changes in the proportion of WNND cases.

Because diagnosis of WNV fever is tricky and thus results in variable reporting from year to year, the ratio of WN fever to WNND is difficult to determine and is often misinterpreted.
9. Can West Nile virus outbreaks be prevented?

Practically speaking, the only way to prevent WNV outbreaks is to maintain vigilant surveillance of local mosquito populations and implement effective mosquito control when infections are detected. These public efforts, coupled with individual efforts to avoid mosquito bites, are the best means of WNV control.

Surveillance starts with trapping mosquitoes across cities and counties and regularly testing those mosquitoes for the presence of WNV. The problem is that mosquito surveillance is often spotty and the same places aren’t tested at consistent intervals. For surveillance programs to be effective, consistent coverage is needed, as well as good historical data. Because these programs can test trapped mosquitoes for other viruses besides WNV, the surveillance infrastructure is important for a multitude of public health threats. Surveillance efforts can also include citizen participation by encouraging people to be on the lookout for sick or dead birds. These birds can be tested for the presence of WNV; dead birds are often a more visible indication of the virus’s presence in an area than mosquito populations.

When increasing numbers of infected mosquitoes are detected, integrated pest management programs can be implemented to keep those mosquito populations below a level that permits WNV amplification. Egg-laying can be prevented in standing water simply by eliminating breeding pools. However, in large cities, the number of available breeding grounds can be enormous (think of all the storm drains and sewers)! Insecticides to kill mosquito larvae can be applied to water sources, but the treatment needs to occur at the perfect time — just as it gets warm. If applied too early, the larvae may not be present and the water may be too cold for the active ingredients to work properly. Insect growth regulators that disrupt metamorphosis or surface films to suffocate the larva also can be used. Larvae can be further targeted by releasing fish to eat them. Once WNV infections have been detected in mosquitoes, birds, or humans, spraying of insecticides is the only way to remove infected adult mosquitoes.

Protecting the blood supply:

A critical aspect of WNV surveillance is blood bank screening. After evidence surfaced in 2002 that WNV might be transmitted through blood transfusions, the Food and Drug Administration (FDA), the blood testing community and biotechnology manufacturers moved quickly to develop specific tests to detect WNV-infected units of blood and prevent them from entering blood bank supplies. Screening donors for WNV is particularly important since the majority of people infected with WNV do not develop symptoms. In a model for collaboration between industry and government, WNV tests were developed by Roche and Gen-Probe and blood screening for WNV was under way by June 2003, less than a year after the problem was first detected! Since routine testing began, thousands of blood donations contaminated with WNV have been detected and removed from the blood supply, and transfusion transmission of WNV is now exceedingly rare.
Although the idea of spraying often brings up bad collective memories of rampant DDT use in the 1950s and 1960s, techniques used today are much more targeted and effective, aiming to reduce the impact on non-target species.

Surveillance and treatment efforts largely fall to municipal and state services, but by changing your own behavior and using protective measures consistently, you can reduce your risk of being bitten by infected mosquitoes. Individuals can protect themselves by avoiding outside activities at dusk when mosquitoes are at their most active, wearing long clothing to cover exposed skin, using insect repellent sprays, and cleaning up potential mosquito breeding habitats on personal property. By literally taking matters into your own hands, you can protect yourself from WNV.

Unfortunately, there is no treatment for WNV disease beyond supportive care and as yet, no vaccine exists for humans. This is why surveillance and preventative measures are so important. While developing a vaccine to WNV is scientifically possible, technical and economic considerations have prevented pursuit of this research in earnest. Because WNV cannot spread from human to human, it does not risk widespread epidemics on the scale of influenza, and those outbreaks which do occur are scattered and sporadic, complicating the design of large scale clinical trials. Thus, drug companies are discouraged from investing large sums of money on their own for vaccine development and clinical efficacy trials. Another approach might be to direct research towards therapeutics that can be deployed once an outbreak is underway.

An effective vaccine would protect people from disease, but would do nothing to halt the spread of West Nile virus in the environment since the virus already cannot be passed from person to person. Vaccinating key bird species might play a more decisive role in preventing disease transmission, although this practice is rather impractical — avian vaccination is simpler when limited to preventing threatened endangered species from going extinct, like condors and cranes.
