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## Review Article

# West Nile virus infections are here! Are we prepared to face another flavivirus epidemic?

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**Abstract**

Emerging arthropod-borne viruses (arboviruses), such as chikungunya and Zika viruses, are a major threat to public health in countries like Brazil where biodiversity is high and medical care is sometimes precarious. West Nile fever is a disease caused by the West Nile Virus (WNV), an RNA virus belonging to the *Flaviviridae* family. It is transmitted by infected mosquitoes to numerous animals like birds, reptiles and mammals, including human and non-human primates. In the last decade, the number of reported cases of WNV infection in humans and animals has increased in the Americas. Circulation of WNV in forests and rural areas in Brazil has been detected based on serological surveys and, in 2014, the first case of West Nile fever was confirmed in a patient from Piauí State. In 2018, the virus was isolated for the first time from a horse from a rural area in the state of Espírito Santo presenting with a neurological disorder; this raises the possibility that other cases of WNV encephalitis may have occurred without clinical recognition and without laboratory diagnosis by specific assays. The imminent WNV outbreak poses a challenge for Brazilian clinicians and researchers. In this review, we summarize the basic biological and ecological characteristics of this virus and the clinical presentation and treatment of febrile illnesses caused by WNV. We also discuss the epidemiological aspects, prophylaxis of WNV infections, and monitoring strategies that could be applied in the possibility of a WNV outbreak in Brazil.

**Keywords:** West Nile virus (WNV). Arbovirus. Outbreak. Surveillance.

## BACKGROUND

The West Nile virus (WNV) was first isolated in 1937 from a patient presenting with a febrile disease residing in the West Nile district in northern Uganda[1,2]. The first documented WNV epidemic occurred in Israel in 1951 with young children representing the majority of cases[3]. The disease was mild, with no reported fatalities, and it was the first time that the main clinical manifestations were thoroughly described, and consisted mainly of fever, headache, anorexia, exanthema, myalgia, abdominal pain, and vomiting. Lymphadenopathy, sore throat, and diarrhea occurred occasionally. Outbreaks in Egypt, occurred between 1951 and 1954, also led to a better understanding of the various clinical and epidemiologic aspects of the virus[4,5]. Studies performed in the Nile Delta region demonstrated that the virus was infectious in a wide range of species, including birds and non-human mammals, and that WNV was endemic along the Nile, with a 60% seroprevalence rate in humans[5]. The WNV arthropod-borne nature was suggested in 1943 and later characterized as one of the most widespread arboviruses since more than 65 mosquito species have been shown to be infected by WNV[6].

Until the 1990s, WNV was considered to be an old world flavivirus but, in 1999, it was detected in the United States of America and caused a high mortality in both free-living and captive birds in the New York zoos[7-9]. In that same year, 67 people were affected, 21 of which died. The virus subsequently spread to practically all the states of the USA, affecting birds, horses and humans[10-14]. Over the past three decades, WNV has

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become a concern for both public health and veterinary medicine in Europe and the Americas[15,16]. Virus circulation has also been detected in other regions of the world, such as Africa, the Middle East, Mediterranean Europe, India, Asia , and Australia.

Serological evidence of WNV circulation in animals in South America was first documented in Colombia in 2005 in horses that had likely been infected with WNV in 2004, and then in Argentina in 2006 in horses that died from encephalitis that same year. However, it was later shown that WNV may have been introduced into Argentina in 2004[17-19]. In Venezuela, WNV was detected in sylvatic birds in 2006 and in horses in 2004[20]. However, only the Argentinean report presented evidence for an equine neurological disease associated with the WNV[19]. Serological evidence of WNV infection in Brazilian horses and birds has been reported from animal sera collected since 2008 from the Central and Western Brazilian regions, particularly the Pantanal region[21-24]. Serological evidence of WNV circulation in Brazil outside of Pantanal was reported in 2013, namely in Paraiba State, suggesting that WNV was spreading towards the northeast part of the country[25]; this spread was confirmed in 2014 with the description of the first human case of WNV infection. The patient was a rural worker from Piauí State (Northeast region) that presented clinical symptoms of acute encephalitis[26]. The first isolation of WNV in Brazil was documented in 2018 when the virus was isolated from the central nervous system (CNS) of a dead horse with neurologic manifestations. The sample from this animal was collected in a rural area of Espírito Santo State, further confirming the spread of this virus to different Brazilian regions, as depicted in **Figure 1**[27].

## THE VIRUS

WNV belongs to the *Flaviviridae* family and the genus *Flavivirus* which contains more than 70 species of viruses that can be divided into tick-borne and mosquito-borne virus groups[28,29]. The mosquito-borne viruses can be further subdivided into the encephalitic clade (or the Japanese encephalitis virus (JEV) serocomplex), which includes WNV, St. Louis encephalitis virus (SLEV), and JEV; and the non-encephalitic or hemorrhagic fever clade, which includes the dengue virus (DENV), Zika virus (ZIKV), and yellow fever virus (YFV)[29]. The geographic distribution of the mosquito-borne flaviviruses depends largely on the habitat of the preferred mosquito vector.

Like all mosquito-borne flaviviruses, WNV is a positive-sense, single-stranded RNA virus, with a genome of approximately 11,000 nucleotides. The viral RNA is translated into a single polyprotein which is processed by cellular and virus proteases, giving rise to three structural (envelope [E], pre-membrane/membrane [prM/M], and nucleocapsid [C]) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)[30]. Following a bite of an infected mosquito, WNV enters cells by clathrin-mediated endocytosis and the low pH inside the endosome generates a conformational change in E glycoprotein, leading to the fusion of the virus envelope with the endosome membrane and the subsequent release of the viral genome into the cytoplasm[31,32]. Virus replication starts as soon as the RNA genome is released into the cytosol and virion assembly begins with membrane components derived from the endoplasmic reticulum (ER)[30]. During virus release from infected cells, the prM protein is cleaved by the cellular protease furin, which is very important for virus infectivity, and this cleavage turns immature particles into mature ones that are then released into the extracellular space[30].

## TRANSMISSION CYCLE

The classic WNV transmission cycle involves birds as well as mosquitoes primarily of the genus *Culex*, such as *Cx. pipiens* and *Cx. restuans*; other species like *Aedes albopictus* and *Ae. vexans* are considered potential vectors[33-35]. These *Culex* species represent the primary vectors in enzootic/epizootic transmission; other species, like *Cx. salinarius* and *Aedes*/*Ochlerotatus* spp., serve as bridge vectors for humans and horses[34]. From 1999 to 2017, the Centers for Disease Control and Prevention (CDC), in the USA, detected WNV in several mosquito species of the genera *Anopheles*, *Coquillettidia*, *Culiseta*, and *Psorophora*. The ability to infect several mosquito species could be related to the high host species diversity, leading to many different transmission cycles[36]. New hypotheses about the maintenance cycle of WNV have generated a broader view of the classical WNV transmission cycle, involving the house sparrow - *Cx. pipiens* - house sparrow, in which several species of vectors (mosquitos and ticks) and hosts (birds and small rodents) are also involved[37]. However, it is unclear how the mosquito population influences the timing and intensity of avian epizootics and human epidemics[38].

Some species of birds from the orders Passeriformes (songbirds), Charadriiformes (shorebirds), Strigiformes (owls), and Falconiformes (hawks) can act as reservoirs and amplifiers of the virus due to the high and prolonged viremia[23,33,39,40]. However, in the order Passeriformes, the mortality rates can exceed 40%[40]. In addition to birds, WNV can also infect humans, horses, non-human primates, and various other mammalian species. Ectothermic animals, such as reptiles and amphibians, can also become infected by WNV, attaining sufficient levels of viremia to infect mosquitoes[40-45]. Human and equine hosts are considered accidental/terminal hosts because the viremia is short and insufficient to infect mosquitoes, thus ending the transmission cycle[23]. Although the transmission cycle is well understood in the United States[36,37,39], the exact nature of WNV transmission cycle in Brazil is not known; but based on the species that were positive for the virus by serology or PCR in Brazil, as well as on the transmission cycle reported in other countries[37], a model can be proposed for the probable WNV transmission cycle in Brazil, as depicted in **Figure 2**.

*Culex quinquefasciatus* and *Ae. albopictus* mosquitoes are highly abundant and widely distributed in Brazil, and are an important risk factor for the transmission of the WNV in Brazil as their WNV infection produce high enough viremia levels to transmit the virus. Consequently, the Brazilian Ministry of Health released a guideline in 2011 for the surveillance of *Cx. quinquefasciatus*[46]. Although WNV transmission is carried out primarily through mosquito bites, other routes such as blood transfusion and organ transplantation can also

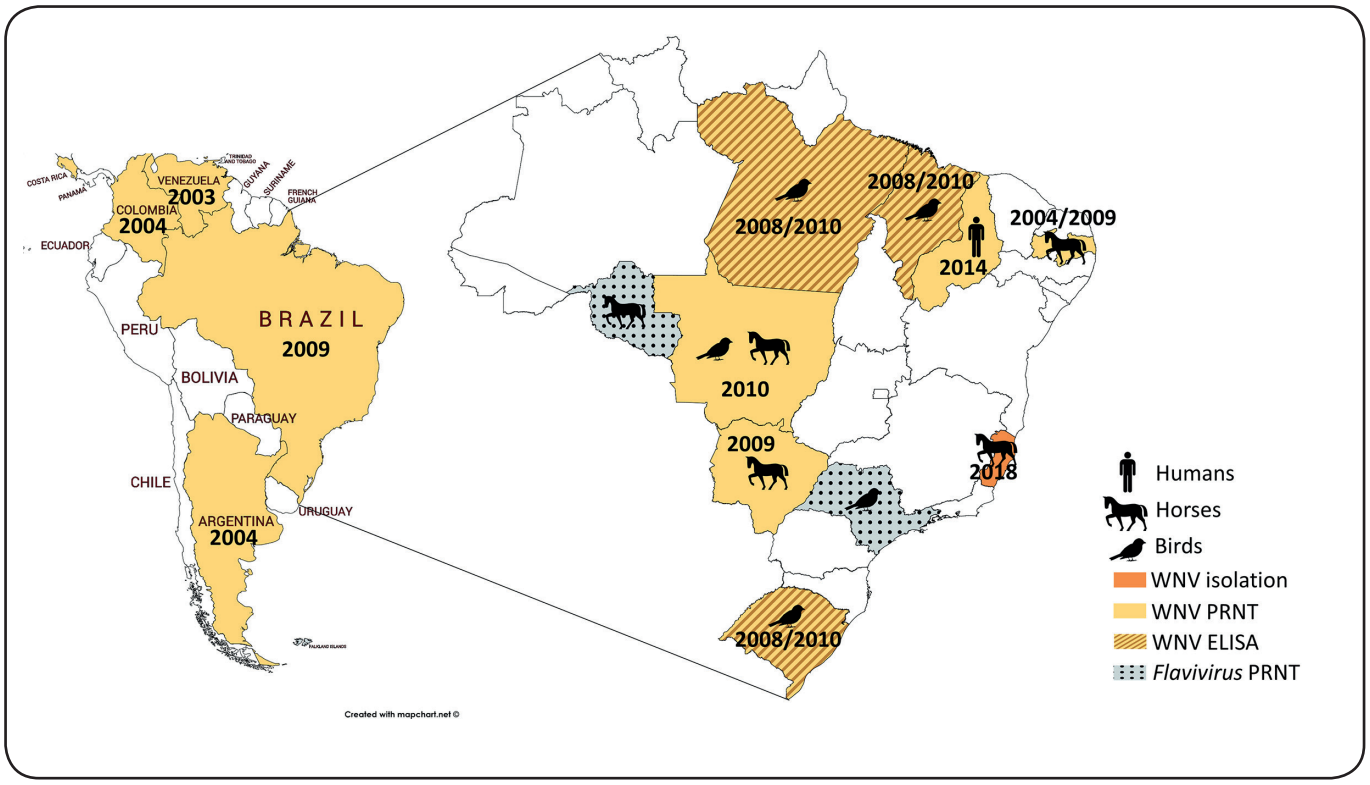


**FIGURE 1:** West Nile virus dispersion in South America and Brazil. Site, year of sampling, and infected host are represented. The diagnostic tools applied are indicated by different colors, as follows: virus isolation and PCR (orange), serologic detection by a plaque-reduction neutralization test (PRNT90 or PRNT80; light orange), serologic detection by ELISA (light orange with stripes), and undefined Flavivirus by PRNT90 (gray with dots).

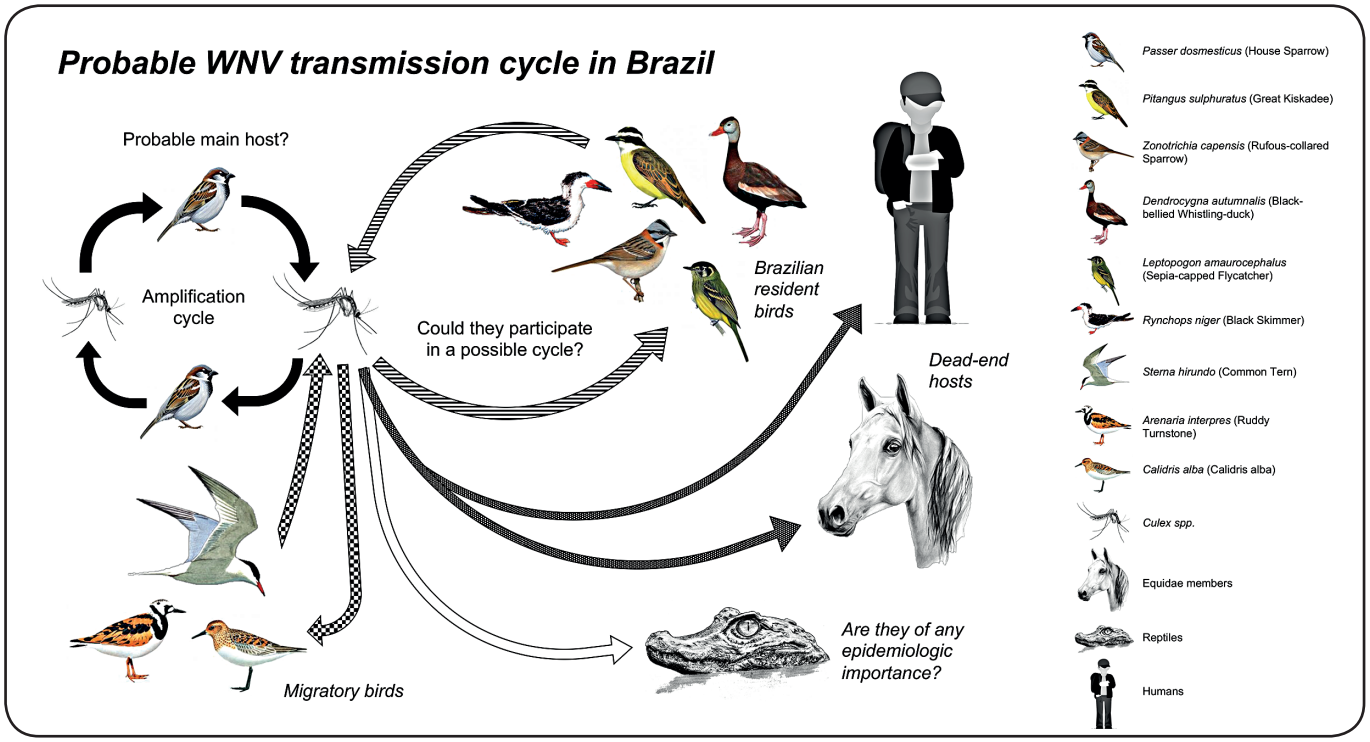


**FIGURE 2:** The probable WNV transmission cycle in Brazil. Black arrows: possible, but not confirmed, WNV cycle amplification. Black arrows with white spots: confirmed transmission cycle to dead-end hosts. White arrows with black lines: native birds with laboratory, serological, and/or molecular evidence of WNV. White arrows with black squares: native birds of the northern hemisphere that migrate to Brazil, in which West Nile infection has been confirmed. White arrow: no evidence has been found in Brazil, but some cases have been confirmed in other countries. Images sources 54-63.

represent a threat, mostly for immunocompromised people[47-49]. Vertical transmission during pregnancy, perinatally, or through breastfeeding, although possible, do not appear to represent an important transmission route[50-53].

## CLINICAL MANIFESTATIONS IN HUMANS

In humans, WNV infection is predominantly subclinical. It is estimated that only 20% of infected patients develop symptoms after an incubation period ranging from 3 to 15 days[35,64]. When symptomatic, the clinical manifestations may range from fever and myalgias to meningoencephalitis and death[65]. The majority of symptomatic cases in humans infected with WNV present with an acute febrile illness called West Nile fever that is characterized by an abrupt onset of fever, malaise, loss of appetite, headache, myalgia, fatigue, ocular pain, nausea, vomiting, and lymphadenopathy[40,66]. A maculopapular, non-pruritic rash can often occur in the extremities, palms, soles, and torso; the rash usually occurs on days 5-12 of the disease, lasts for approximately one week, and resolves without scaling[67]. West Nile fever is usually a mild illness and although symptoms may last a few days, they can also persist for weeks, causing a debilitating illness[66].

Less than 1% of infected individuals develop a neuroinvasive disease characterized as meningitis, encephalitis, poliomyelitis-like syndrome or acute flaccid paralysis. Patients with West Nile meningitis can present with fever or hypothermia, headache, photophobia, and gastrointestinal symptoms, like nausea, vomiting, and diarrhea, and meningeal signs, such as nuchal rigidity, Kernig and/or Brudzinski signs[68]. Individuals with West Nile encephalitis can present either a mild illness, with symptoms that include fever or hypothermia, headache, nausea, vomiting, tremors, weakness, and confusion; or a more severe illness characterized by encephalopathy and death[69]. Patients with West Nile encephalitis also present with extrapyramidal disorders, myoclonus mainly during sleep, and characteristics of Parkinsonism[70-72]. Magnetic resonance imaging (MRI) is more helpful than computerized tomography in detecting central nervous system inflammation, as up to one-third of patients undergoing MRI showed acute meningeal enhancement consistent with encephalitis. Cerebrospinal fluid analyses usually show a normal glucose level, increased protein concentration, and a lymphocytic pleocytosis ranging from 10-100 cells/mm$^3$.

West Nile-associated neurologic diseases can also manifest as a poliomyelitis-like syndrome and acute flaccid paralysis characterized mainly by muscle weakness that, in most cases, evolves to respiratory failure[73,74]. Although neurological diseases associated with WNV infections can arise at any age, the elderly and immunocompromised patients, like those with cancer, diabetes, hypertension, kidney disease, and transplant recipients, are at greater risk[75,76]. The case fatality rate is higher in elderly people, especially those over 65 years of age.

These diseases occur due to the ability of WNV to cross the blood-brain barrier (BBB) and infect the CNS through dissemination by axonal transport. The replication of the WNV in neurons, astrocytes, and microglia triggers the release of immune mediators by these cells, resulting in increased BBB permeability, inflammation of the meninges, damage to CNS cells, and consequently, CNS diseases[77-79]. WNV-associated neurologic illnesses do not necessarily correlate with a bad outcome, as some patients with initial severe encephalopathy and associated coma can show a good recovery and minimal sequelae[69]. Following acute illness, approximately 40% of patients experience persistent symptoms for over a year, including fatigue, muscle aches, headaches, movement disorders, and difficulties with memory and concentration[80,81]. Patients with severe West Nile encephalitis may require assistance with daily activities following hospital discharge[82,83].

## CLINICAL MANIFESTATIONS IN ANIMALS

West Nile infections in animals cause a very similar disease to the one seen in humans. The clinical signs vary according to which animal species is infected from among all species that can be infected by the virus and succumb from the disease; the most affected animals are birds (mainly exotic) and horses[84,85]. Some bird orders, i.e., the Passeriformes, Charadriiformes, and Falconiformes, are considerably more prone to developing disease than others, like the Galliformes, that can be infected but do not manifest any clinical signs[85,86]. In species belonging to Galliformes order, the clinical signs may be nonspecific and include depression, lethargy, erect feathers, anorexia, rapid weight loss, and neurological signs such as ataxia, paralysis, tremors, pedaling movements, circling, swimming in circles, abnormal head posture, torticollis, nystagmus, seizures, opisthotonos, and death[87-90].

Among mammals, squirrels, chipmunks, bats, dogs, cats, white-tailed deer, reindeer, sheep, alpacas, non-human primates, horses, harbor seals, dromedary camels, and some others can be infected by WNV, but only a small number will manifest clinical signs and become ill[85,91,92]. After humans, horses are the mammals that are most affected by WNV as they can develop a disease with the same level of severity[88,93]. The incubation period of the West Nile infection in horses is estimated at 3 - 15 days, similar to that seen in humans[84,94-97]. Like humans, most infected horses do not manifest any clinical signs, but a small percentage can develop encephalitis and die[88,98]. Other clinical signs include depression, loss of appetite, colic, limb weakness, recumbency, and muscle fasciculation[27,84,93,98-101]. A neurological syndrome may set in, manifesting as ataxia, stupor, behavioral changes, paralysis of one or more limbs, lateral decubitus, intense sweating, pedaling movements, seizures, and cranial nerve palsy opisthotonos, as well as other alterations like hemineglect[27,93].

## DIAGNOSIS AND TREATMENT

Clinical manifestations alone are insufficient to confirm the diagnosis of West Nile disease since most common clinical signs of symptomatic WNV infection are similar to those of other flavivirus infections. However, differently from other flaviviruses such as DENV and ZIKV, severe WNV infection is accompanied by neurological signs. Patients with severe WNV disease usually present with a febrile disease accompanied

by neurological manifestations like meningitis, encephalitis, meningoencephalitis, and flaccid paralysis of unknown etiology, but compatible with a viral disease[102]. Diagnosis can be made during the viremic phase of infection, with high sensitivity and specificity, through the detection of viral RNA in the blood, urine, and cerebrospinal fluid (CSF) by quantitative Real-Time Polymerase Chain Reaction (RT-qPCR). However, it is not routinely used because West Nile infection usually has a short-lived viremia[103,104]. Consequently, detection of IgM antibodies by enzyme-linked immunosorbent assay (ELISA) in serum or CSF, collected 5 or 8 days after the onset of symptoms, respectively, is routinely used for diagnosis, indicating recent infection, although cross-reactivity may occur[105]. To validate the results, a neutralization assay, considered to be the gold standard test, can be performed to detect neutralizing antibodies. Antibody detection can also be performed using an immunofluorescence assay[105,106]. In *postmortem* patients, immunohistochemical assays of brain tissue samples can be carried out to detect antigens in fixed tissues[107].

Patients diagnosed with uncomplicated West Nile disease usually do not require specific intervention, needing only adequate hydration and pain management. However, the patients most at risk, such as the elderly and immunocompromised patients, need close monitoring to quickly detect the progression to a more severe neuroinvasive disease. If seizures and increased intracranial pressure are present, they should be managed under intensive care, paying special attention to the level of alertness[108]. West Nile virus infection may not be initially suspected in patients with a West Nile neurologic disease characterized as meningitis or encephalitis, but should be suspected in patients developing acute asymmetric paralysis[108]. Diagnosis of WNV infection might be difficult in areas where other flaviviruses circulate, but a high level of suspicion must be in place, especially by the combination of epidemiologic features and clinical manifestations.

The design of specific anti-viral therapies represents a challenge because WNV viremic period in humans is short and the virus infection is generally cleared shortly after disease onset[108]. Treatment trials with interferon-α have not suggested a clear benefit even though it has a protective effect *in vitro* and was shown to improve convalescence in a case study of two WNV patients with encephalitis[109,110]. Treatment of animal models with either WNV-specific intravenous immune globulin (IVIG) from pooled donors or humanized monoclonal WNV antibodies has shown good efficacy if treatment is started prior to, or shortly after disease onset. However, a reliable efficacy assessment in human randomized clinical trials has been difficult to obtain[111-116].

## SURVEILLANCE AND PREVENTION

Therapeutic approaches against WN disease are mainly supportive since there are no approved vaccines or specific antiviral treatments available for human use[108,117]. However, successful strategies to prevent WNV infections have already been developed in veterinary practice. There are four USDA-licensed vaccines available for equines that confer immunity for at least one year[118]. The West Nile-Innovator DNA vaccine was developed by Fort Dodge Animal Health in 2005 for use in horses and became the first licensed DNA vaccine, but was later removed from the market[119]. The current approved equine vaccine formulations consist of inactivated whole WNV (two vaccines), a nonreplicating live canarypox recombinant vector vaccine, and an inactivated flavivirus chimeric vaccine[118]. Since these vaccines were licensed, the incidence of West Nile diseases in horses have declined in the USA[120,121]. Vaccine formulations are also being developed for non-human primates and small mammals. Potent induction of neutralizing antibodies against WNV infections in non-human primates has been observed with live-attenuated WNV vaccine strains, developed either by site-directed mutagenesis or chimerization, where WNV genetic material is inserted into a yellow fever virus vaccine strain backbone[122,123]. Subunit and DNA vaccines have also been developed to protect small animals and have provided good protection against viral infection[124,125].

Until a WNV vaccine designed for human use is commercially available, the most effective prophylaxis against WNV infection remains vector control and the use of insect repellents to prevent the bites of infected mosquitoes. Furthermore, considering the evidence for viral circulation among several animal species, confirmation of a human case of WNV infection in Brazil in 2014, and WNV isolation in 2018, the epizootic surveillance system must remain in place and in close association with active reporting of human cases[126]. Cases of encephalitis, meningitis, and other diseases that affect the CNS without a clear etiology, either in animals or humans, should always include West Nile neurologic disease in the differential diagnosis. Reporting and testing dead birds for the presence of WNV infections are important resource for surveillance programs. Entomological and sentinel animal surveillance regimens must be continuously carried out aiming at early identification of viral circulation[126]. Active surveillance for WNV infections in mosquito and bird populations, in combination with climate and environmental data analysis, may also allow for the detection of WNV prior to disease onset in equine or human populations, and thereby predict the time and sites of future WNV-associated disease outbreaks[105].

The introduction of exotic diseases, whether zoonotic or not, in new territories such as Brazil is inevitable since globalization allows for the translocation of pathogens to occur at speed not previously experienced in the past. In addition, Brazil has a high diversity of hosts and vectors that allows the maintenance and perpetuation of new viruses with previously unknown cycles. Therefore, implementing active surveillance in strategic areas of the country is necessary for the early detection of new pathogens and to restrain their entry and dissemination, mitigating as much as possible the establishment of enzootic cycles and avoiding losses in public health and in the economy.

## CONCLUSIONS

WNV is considered an emerging virus throughout Latin America. A pioneer sentinel surveillance system for encephalitis and other neurological syndromes has been implemented in Piauí State, Brazil, since 2013. According to the Brazilian Ministry of Health, 285 suspected cases have been investigated in the

region. In 2014, a patient was diagnosed with WNV infection and, in 2017, 10 suspected cases of neuroinvasive disease were reported, although diagnosis has yet to be confirmed[127]. In a note released on February 8, 2019, the Secretary of Health (SESAPI) for Piauí State confirmed one additional human case of WNV in that state in 2017, where the patient presented with acute muscular flaccid paralysis[128,129]. With the recent increase in suspected cases in that region and the first isolation of WNV from an infected horse in Espírito Santo State, many investigators and health professionals are concerned with the possibility that WNV establish itself in Brazil. Considering that most patients are asymptomatic and symptoms of West Nile disease are very similar to those of other viral infections, without an adequate degree of suspicion the number of cases of West Nile fever could go unnoticed and outbreaks may occur in areas considered free of WNV circulation. The widespread lack of capacity for molecular or serological diagnosis specific to WNV infections in hospitals and clinical laboratories prevents the acquisition of the knowledge on the true number of infected individuals.

Because mosquitoes found throughout Brazil, such as those of the genera *Culex* and *Aedes*, can transmit WNV, there is a growing concern that the virus may spread itself to the whole country. The *Culex* genus is abundant in Brazil and its life cycle is based on water bodies with a high burden of organic material; as such, vector control is extremely important in areas where the basic sanitation is deficient or absent, presenting a higher risk for WNV transmission. Considering the reservoirs of migratory birds present in Brazil and the potential availability of new animal reservoirs due to the vast size of the Brazilian biome, it is only a matter of time before the WNV spreads across the country once its replication cycle has been established in the environment, as it was observed following its emergence in the United States. Mammals presenting with neurological syndromes and birds that die without a definite cause or are found dead should both be investigated for WNV infection. Finally, it is necessary to increase active epidemiological surveillance in animals and humans and promote preventive actions to minimize the possibility of WNV infection in humans before it becomes a major public health issue, as occurred with other arbovirus infections such as dengue, zika, chikungunya and, more recently, the sylvatic resurgence of yellow fever virus.

**Conflict of Interest:** The authors declare no conflicts of interest.

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