

Review Article

The Global Ecology and Epidemiology of West Nile Virus

Caren Chancey, Andriyan Grinev, Evgeniya Volkova, and Maria Rios

United States Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD 20993-0002, USA

Correspondence should be addressed to Maria Rios; maria.rios@fda.hhs.gov

Received 24 June 2014; Accepted 10 August 2014

Academic Editor: Michael J. Conway

Copyright © 2015 Caren Chancey et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Since its initial isolation in Uganda in 1937 through the present, West Nile virus (WNV) has become an important cause of human and animal disease worldwide. WNV, an enveloped virus of the genus *Flavivirus*, is naturally maintained in an enzootic cycle between birds and mosquitoes, with occasional epizootic spillover causing disease in humans and horses. The mosquito vectors for WNV are widely distributed worldwide, and the known geographic range of WNV transmission and disease has continued to increase over the past 77 years. While most human infections with WNV are asymptomatic, severe neurological disease may develop resulting in long-term sequelae or death. Surveillance and preventive measures are an ongoing need to reduce the public health impact of WNV in areas with the potential for transmission.

1. Introduction

First described in 1937 from a febrile illness case in Uganda, West Nile virus (WNV) caused infrequent outbreaks typically associated with mild febrile illnesses from the 1950s through the 1980s in Israel, Egypt, India, France, and South Africa [1–11]. The first outbreak of neuroinvasive disease caused by WNV (WNND) was reported among the elderly in Israel in 1957 [6, 11]. Subsequent outbreaks included adult and pediatric WNND cases [4, 5, 9, 12, 13].

Starting in the mid-1990s, the frequency, severity, and geographic range of WNV outbreaks increased, and outbreaks of WNV meningitis and encephalitis affecting primarily adults struck Bucharest, Romania, in 1996, Volgograd, Russia, in 1999, and Israel, in 2000 [14–16]. WNV crossed the Atlantic and reached the western hemisphere in the summer of 1999 when a cluster of patients with encephalitis was reported in the metropolitan area of New York City, New York, in the United States, and within 3 years the virus had spread to most of the contiguous U.S. and the neighboring countries of Canada and Mexico. In addition, although few human cases have been reported, WNV has also been found in Central and South America through surveillance studies in field specimens, suggesting a potential risk for an outbreak in humans [17, 18]. In the 77 years since its discovery, the virus has propagated to a vast region of the globe and is

now considered the most important causative agent of viral encephalitis worldwide (Figure 1).

2. Viral Genome and Structure

WNV belongs to the genus *Flavivirus*, family *Flaviviridae*, and is a member of the Japanese encephalitis serocomplex, which also includes Japanese encephalitis virus, St. Louis encephalitis virus, Rocio virus, and Murray Valley encephalitis virus [19, 20]. Like other flaviviruses, WNV has a single-stranded positive-polarity RNA genome of approximately 11 kb, containing 10 genes flanked by 5' and 3' noncoding regions (NCR) with no polyadenylation tail at the 3' end [21–25]. The NCRs of the WNV genome form stem-loop structures essential for viral replication [26, 27]. The viral genome encodes a single polyprotein that is co- and posttranslationally cleaved into 3 structural proteins: Capsid (C); Pre-M/Membrane (prM/M); and Envelope (E); and 7 nonstructural (NS) proteins: NS1; NS2A; NS2B; NS3; NS4A; NS4B; and NS5 [24, 28] (Figure 2).

Structurally the WNV virion is a ~50 nm icosahedral particle, surrounded by a lipid bilayer (reviewed in [29]). The nucleocapsid is composed of C protein, which associates with the RNA genome and mediates viral assembly [30, 31]. Heterodimers of prM and E protein become embedded in

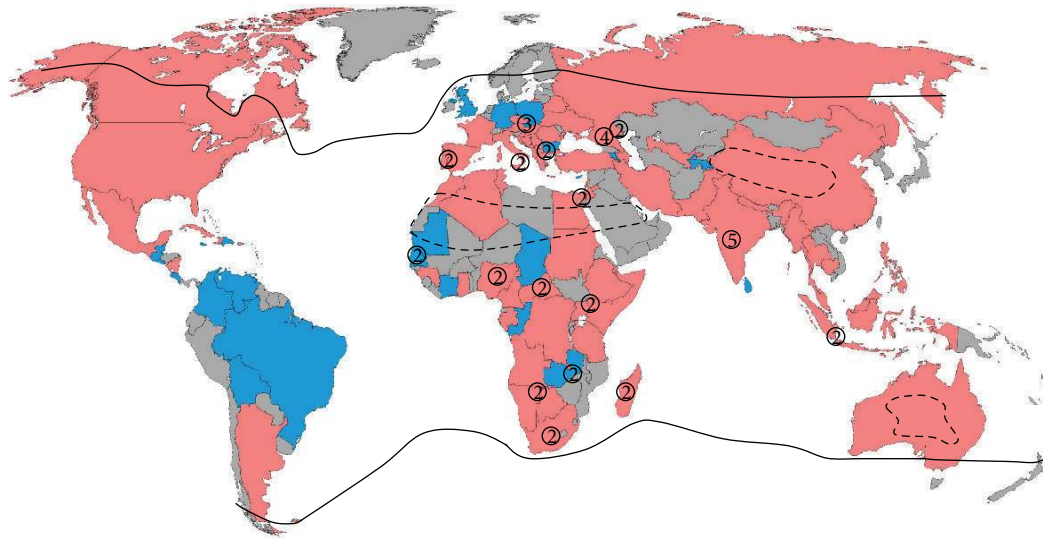


FIGURE 1: Global distribution of WNV by country: Red—human cases or human seropositivity; Blue—nonhuman/mosquito cases or seropositivity; Gray—no data or no positives reported. Black lines represent worldwide distribution of the main WNV mosquito vectors, excluding areas of extreme climate denoted by dashed lines. Circled numbers indicate the reported presence of WNV lineages other than lineage 1 in that specific area. For Japan, South Korea, Finland, and Sweden, seropositivity for WNV has been detected only in nonresident birds, which was not considered indicative of local transmission. Kading et al. [182] reported infections in gorillas living near the border of the Democratic Republic of the Congo and Rwanda, which were sampled in the D.R.C., but may have been infected in Rwanda.

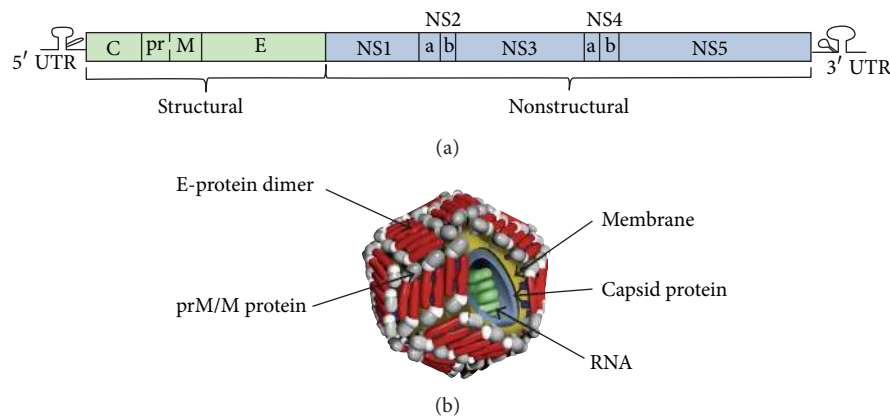


FIGURE 2: WNV genome organization and virion composition: (a) the viral genome is represented with one ORF encoding 3 structural and 7 nonstructural proteins. The 5' and 3' UTRs are indicated. Structural proteins are colored green, whereas nonstructural proteins are blue. (b) Structure of WNV virion.

the lipid bilayer of the virus during assembly and are exposed on the virion surface [32]. The prM protein is thought to protect the immature virion from undergoing premature fusion prior to viral budding from the cell surface by blocking the fusion loop of E and is cleaved off during the viral maturation process [32–36]. During infection, mature, immature, and partially mature virus particles are produced, containing a varying number of immature prM protein molecules on the surface [37]. The E protein mediates both binding of the receptor on the cell surface for viral entry and fusion with the membrane of the host cell [38–40].

The seven nonstructural proteins are multifunctional, playing critical roles in viral RNA synthesis and/or assembly.

NS1 is believed to play an early role in regulation of viral replication [41–43]. NS3 has multiple enzymatic functions, serving as a viral serine protease which cleaves the other nonstructural proteins from the viral polyprotein, in association with NS2B; an RNA helicase in association with NS4a; and an NTPase in association with NS5 [44–49]. The NS5 protein is necessary for viral replication, containing RNA-dependent RNA polymerase (RdRp) activity in the C-terminal region and methyltransferase activity in the N-terminal region [41, 50–53]. NS2A, NS2B, NS4A, and NS4B are small, hydrophobic proteins that have no known enzymatic functions, but are believed to act as cofactors for viral replication complex assembly and localization [54–57].

The WNV NS proteins can also modulate cell signaling and immune responses [58–67]. In particular, the WNV NS1 protein antagonizes the host's antiviral defenses through inhibition of TLR3 signal transduction and STAT1/STAT2 activation [64, 67]. It has also been shown that NS1 inhibits complement activation through fH and C4b binding, contributing to flavivirus immune evasion [58–60]. Alternatively, cell surface-associated NS1 represents a major target for host antibodies which contributes to clearance of WNV-infected cells through Fc-gamma receptor-mediated phagocytosis [61].

3. Genetic Classification

WNV is a genetically and geographically diverse virus. Four or five distinct WNV genetic lineages have been proposed based on phylogenetic analyses of published isolates [3, 68–73]. Their genomes differ from each other by more than 20–25% and correlate well with the geographical point of isolation (Figure 3). Lineages 1, 2, and 5 of WNV have been associated with significant outbreaks in humans [3, 68, 72, 74, 75]. Lineage 1 is distributed widely throughout the world and consists of two clades: 1a and 1b [76, 77]. Clade 1a includes isolates from Africa, Europe, the Middle East, Asia, and the Americas. Clade 1b is represented by the Australian Kunjin virus (KUNV).

Phylogeographic analysis has shown that the most probable origin of WNV lineage 1a was sub-Saharan or Northern Africa [78]. This clade emerged in the beginning of the 20th century and then spread northwards in the 1970s–80s, mainly following the eastern bird migratory route connecting Northern Africa and Israel with Russia and Central Europe. Later, in the 1990s, a strain of WNV genotype 1a appeared in Morocco and Western Europe, where the virus became endemic, causing small sporadic outbreaks. In 1999, this WNV lineage 1a virus was exported, most likely from the Middle East, to the Americas, where it spread over North America and then to South America, making WNV a global public health problem [78]. Zehender et al. further divided clade 1a into A and B subclades, with most isolates from Western Europe and some from Eastern Europe belonging to subclade A and the remaining Eastern European isolates belonging to subclade B [78].

WNV lineage 2 isolates are historically endemic in sub-Saharan Africa and Madagascar and have caused sporadic zoonotic outbreaks in South Africa [71, 76, 79]. More recently, WNV lineage 2 strains have been associated with bird and human outbreaks in southern and eastern Europe [80]. Lineage 2 WNV was also sequenced from a 2004 Indonesian clinical specimen [81]. It has been suggested that WNV lineage 2 originated in Africa and was introduced into Europe, where it became endemic, on at least two separate occasions during the last two decades [82].

Lineage 3 of WNV is represented by a pair of isolates from mosquitoes collected in the Czech Republic border region near Rabensburg, Austria, in 1997 and 1999, which have been shown experimentally to infect only mosquitoes and mosquito cells [68, 83]. Lineage 4 comprises viruses

circulating in Russia since 1988, including a tick isolate from the south-west Caucasus and a number of isolates from mosquitoes and reptiles in the delta of the Volga river [84, 85]. Lineage 5, formerly considered clade 1c of lineage 1, includes isolates from India from 1955 to the present [3, 72, 86].

Other potential lineages of WNV have been described, including Koutango virus from Africa, a group of isolates from Spain, a variant of Kunjin virus isolated from Sarawak, Malaysia, and a Senegalese isolate [73, 75, 87, 88].

4. Hosts and Vectors

4.1. Hosts. Maintained in nature in an enzootic transmission cycle between birds and mosquitoes, WNV can also infect humans and other vertebrates and cause serious disease and death (Figure 4). Birds are considered the most important hosts for the WNV life cycle because they can develop viremia sufficiently high to infect mosquitoes (reviewed in [89]). Birds in the family Corvidae such as American crows (*Corvus brachyrhynchos*) and blue jays (*Cyanocitta cristata*) become ill or die from WNV, but other birds such as common grackles (*Quiscalus quiscula*) and house sparrows (*Passer domesticus*) develop high viremia with lower mortality rates [90]. American robins (*Turdus migratorius*) and house finches (*Carpodacus mexicanus*) are considered important amplifying hosts in different regions of the U.S. [91]. In addition to birds, at least 30 other vertebrate species, including reptiles, amphibians, and mammals, are susceptible to WNV infection. However, only a few nonavian vertebrates, including brown lemurs (*Lemur fulvus*), lake frogs (*Rana rinibunda*), hamsters, fox squirrels (*Sciurus niger*), eastern gray squirrels (*Sciurus carolinensis*), eastern cottontail rabbits (*Sylvilagus floridanus*), and eastern chipmunks (*Tamias striatus*) have been reported to develop viremia levels expected to support vector transmission [89, 92–98]. Humans and horses may suffer serious disease or death from WNV infection but are considered incidental hosts which do not participate in the WNV lifecycle because they do not develop sufficient viremia to infect mosquito vectors (reviewed in [89]).

Although transmission between hosts by mosquitoes is by far the most common route of transmission, WNV can also be transmitted directly if infected animals or mosquitoes are consumed by susceptible hosts or if susceptible birds come in close contact with cloacal or oral fluids from other birds with high WNV viremia [89].

WNV can also be transmitted between humans by blood transfusion, organ transplantation, transplacental transmission, and via breast milk [99–103]. Although blood donations in the United States have been screened for WNV by nucleic acid testing since 2003, thirteen instances of transfusion-associated transmission have occurred, most recently in 2012 [104–107].

4.2. Vectors. Mosquitoes are the vector for natural transmission of WNV. After a mosquito feeds on an infected competent host, the arbovirus replicates within the mosquito and can then be transmitted to a susceptible host through salivary gland secretions (Figure 4). Compared to related

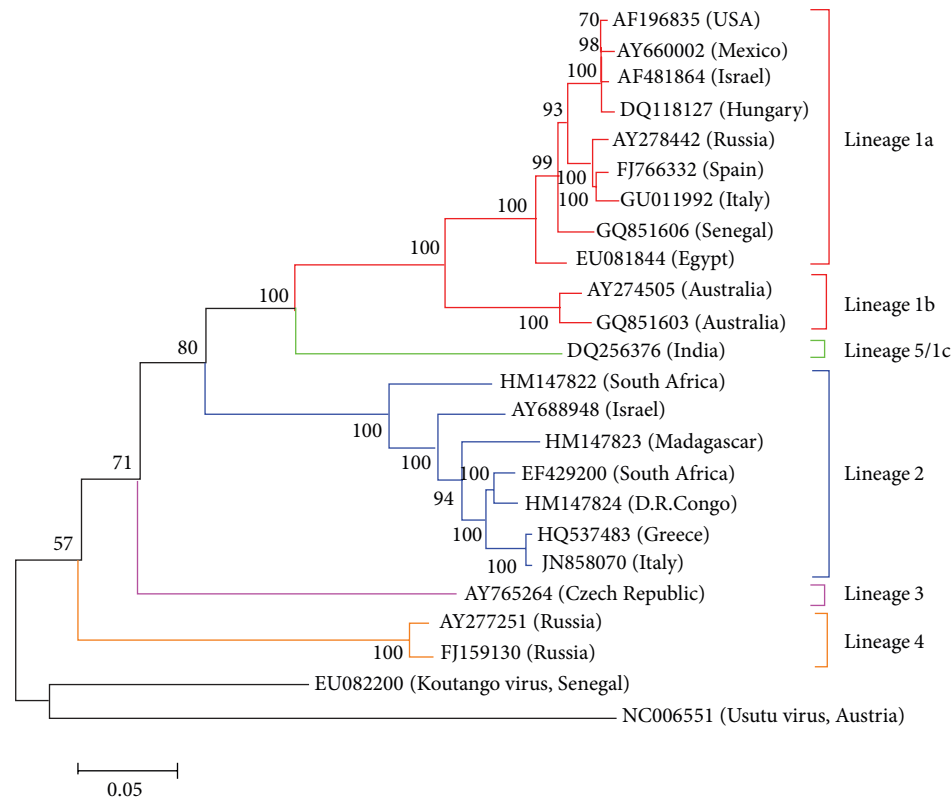


FIGURE 3: Major WNV lineages. Maximum-likelihood phylogenetic tree is based on complete genome sequences and Nearest-Neighbor-Interchange as heuristic search method. The tree was constructed using MEGA 6 with 1000 bootstrap replications. The tree was rooted using Koutango and Usutu viruses.

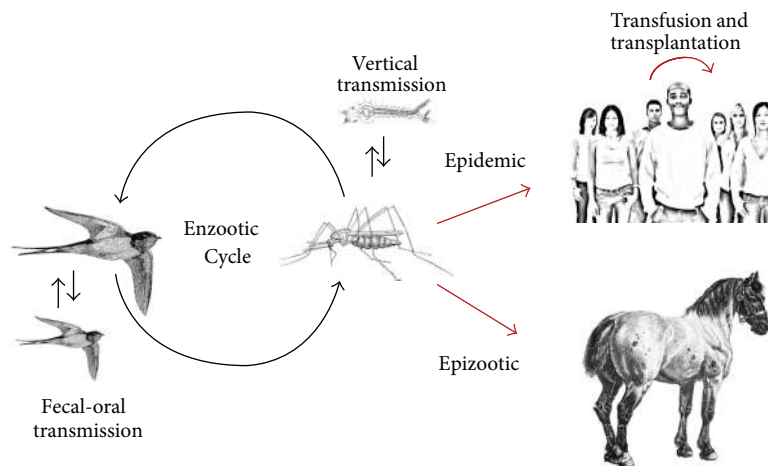


FIGURE 4: WNV transmission cycle: enzootic amplification of WNV by birds and mosquitoes supplemented by bird-to-bird transmission and transmission between cofeeding mosquitoes. Vertical transmission by mosquitoes provides the mechanism of virus overwintering. Humans and horses are counted as incidental dead-end hosts. Human-to-human transmission may come through blood transfusion, organ transplantation, and breast feeding and in utero.

arboviruses such as dengue virus and yellow fever virus, WNV can be transmitted by a variety of mosquitoes with different host-feeding preferences with up to 45 species and 8 genera reported positive in the U.S. between 2004 and 2008 [108]. However, not all mosquito species reported as WNV-positive are competent vectors of WNV, and not all species

that are transmission-competent in the laboratory will play a role in natural transmission [109].

Mosquitoes that feed on both birds and mammals are referred to as bridge vectors for WNV because they act as a “bridge” between an infected reservoir (birds) and mammalian incidental hosts which do not develop sufficiently

high viremia to support transmission to mosquitoes [110, 111]. Ornithophilic mosquitoes play an important role in maintaining and amplifying transmission among birds but typically do not play a role in transmission to humans [109, 111]. Mosquitoes of the genus *Culex* have been reported as the most important bridge vectors in the United States, with *Cx. pipiens* as the dominant bridge vector in the northeastern, north-central, and mid-Atlantic United States, *Cx. quinquefasciatus* in the south and southwest, and *Cx. tarsalis* in the west [110, 112]. *Culex* spp. mosquitoes have also been implicated in transmission in Europe, Australia, and South Africa [113–116]. Mosquitoes of the genus *Aedes*, the transmission vector for related flaviviruses, may also serve as important bridge vectors [108, 109]. While experimental transmission of WNV by ticks has been demonstrated, a role for ticks in natural transmission and maintenance of WNV has not been determined [117–121].

5. Epidemiology and Clinical Outcomes of Human Infections

Most human infections with WNV (~80%) are asymptomatic, and symptomatic infections may vary from flu-like malaise to serious neuroinvasive diseases, for which there is no specific treatment. Fewer than 1% of human infections progress to severe disease, for which the most frequently reported risk factors include advanced age, immune suppression, and chronic medical conditions including, but are not limited to, hypertension, diabetes, and chronic renal failure [122–131]. In 2002, out of more than 4000 cases reported to the CDC, 150 cases were in patients of age 19 or younger. The youngest fatality was a 19-year-old patient, and the median age among fatal cases was 78 years [132]. In the outbreak of 2003, at least 31 cases of WNV encephalitis and 79 cases of WNV meningitis occurred among children and adolescents; however, there were no fatalities caused by WNV disease in children or adolescents [132].

Seroepidemiological studies suggested that one in four to one in five (20–25%) WNV-infected individuals develops mild illness [133, 134] and one person in 150 (0.67%) develops WNND [135]. Subsequent epidemiological studies using asymptomatic infection data obtained from nucleic acid testing to screen blood donations combined with the reported cases to the CDC concluded that one in 244 to one in 353 infections will progress to WNND [123, 136]. These findings suggested that more asymptomatic WNV infections could be identified when prospective studies focused on healthy populations such as blood donors [123, 136]. A serosurvey following lineage 2 WNV infections in Greece in 2010 yielded estimates of one in 124 to one in 141 infections leading to WNND, with approximately 18% of infected individuals showing symptoms [137].

Among WNND patients, 50–71% develop WN encephalitis, 15–35% develop meningitis, and 3–19% develop acute flaccid paralysis [126, 128, 138–145]. Severe cases have fatality rates ranging from 3% to 19% in encephalitis cases [126, 128, 130, 139, 140, 142–144, 146, 147]. Loeb et al. reported that physical and mental impairment resolve in about a year, but

patients with preexisting comorbid conditions take longer to recover [148]. However, other studies of patients infected with WNV have noted physical symptoms and/or cognitive deficits persisting over a year after infection in more than half of WNND cases [141, 149]. Persistence of WNV symptoms >6 months was reported most often in patients with WNND, hypertension, and diabetes [150]. WNND has also been reported as a risk factor for development of chronic kidney disease in a long-term follow-up study of WNV patients [151].

Although fewer cases are available from which to conduct a detailed study, it is thought that both the risk of illness and the risk of neuroinvasive infection are lower from the WNV Kunjin subtype (lineage 1b), which circulates in Australia [152]. Until recently, viruses in lineage 2 were not believed to cause WNND in humans. However, outbreaks of lineage 2 WNV strains in the past 10 years in Russia and Greece have caused WNND and death, with case fatality rates similar to those observed previously for lineage 1 WNV [124, 147, 153]. WNND caused by WNV lineage 2 in horses and humans in South Africa has also been reported [79, 154–156].

6. WNV in Africa and the Middle East

West Nile virus was first observed in Africa, in the West Nile district of Uganda, 1937 [10], and thus had been known in the Old World for over 60 years before it crossed the Atlantic. Though it was first isolated from a febrile human case, WNV was observed to cause relatively mild disease in humans and no deaths were reported from the early epidemics studied [10]. While the introduction and progress of WNV through the New World could be studied as it occurred, epidemics of WNV were believed to have occurred throughout much of Africa, the Middle East, and south Asia before clinical WNV was observed in humans in those areas. A 1939–1940 serosurvey found widespread human seropositivity for WNV, determined by comparison of neutralization titers for WNV, SLEV, and JEV, in Uganda, Sudan, the current Democratic Republic of the Congo, and Kenya, with seropositivity over 50% in some localities [157]. Seropositivity was also found in western Nigeria, in samples collected in 1951 and 1955 [158]. In South Africa, seropositivity in humans who had not traveled, monkeys, domestic animals, and juvenile birds was demonstrated in samples collected in 1954 [159]. Therefore, the past presence of WNV had been demonstrated over a wide geographic range in Africa before clinical infections were observed in most locations.

Following its first isolation in 1937, WNV was not isolated again until 1950. During a serosurvey conducted of 251 individuals, mostly children, living in Cairo, isolates were generated from the serum of three children, only one of whom had been diagnosed with a fever [160]. The same serosurvey noted that more than 70% of the study participants aged 4 and above carried neutralizing and complement-fixing antibodies to WNV and that over 50% of infants carried maternal antibodies against WNV, indicating that WNV infection was widespread among the population and that most individuals were infected as young children [160]. A subsequent serosurvey in northeastern Egypt demonstrated

widespread seropositivity of adults and children at multiple locations in the Nile Valley excluding one coastal location, indicating that WNV was not only endemic in Egypt but frequently transmitted [161]. WNV was also isolated from *Culex* spp. mosquitoes in Egypt in 1952 [162].

The first known isolation of West Nile virus in Israel was from a febrile child in 1951, as part of an outbreak that occurred on an agricultural settlement near Haifa [2]. Morbidity in children in this outbreak was substantially higher than in adults, and subsequent outbreaks in Israel in 1952 and 1953 occurring primarily in adolescents and adults were also identified as WNV, on the basis of isolation of the virus from human cases and serology from human cases and chickens [2, 6, 7]. However, WNV is believed to have been present in Israel prior to these isolations, because prior outbreaks between 1942 and 1950 were observed to have been similar clinically and epidemiologically to the ones in 1951 and 1952 [6]. Illnesses in these cases were generally self-limiting with recovery slower in adults than children [2, 6]. WNV fever was described as a “benign specific short-term fever occurring in epidemic form” and was believed to cause only mild neuroinvasive cases [7]. The first fatalities due to WNND were reported in a cluster of elderly patients in 1957; however, overall, neurological involvement in WNV cases was considered unusual [4, 10, 11, 16]. In 2000, the first WNV outbreak in Israel since 1980 was reported, with 417 serologically confirmed cases and 35 deaths [16]. Viral isolates from this outbreak were most closely related to isolates from the 1996 Romanian and 1999 Russian outbreaks [163, 164]. Since then, Israel has experienced regular annual summertime outbreaks of varying size, similar to those observed in the United States [126, 165–167].

Human seropositivity for WNV in Turkey was documented in the 1970s, and again beginning in the mid-2000s [168–172]. An outbreak of WNV occurred in Turkey in 2010–11, concurrent with other outbreaks in the Mediterranean region, causing 47 cases including 40 WNND cases and 10 fatalities [173].

Seropositivity for WNV was also reported in Iran in the 1970s [174]. A 2008–2009 survey of patients with fever and loss of consciousness identified 3 cases which were positive by RT-PCR and 6 more that were positive by IgG [175]. A study of horses conducted from 2008–2009 identified IgM-positive animals and seroprevalences up to 88% in some regions, with the highest activity in western and southern provinces [176]. Serologic evidence for infection has also been found in Jordan and Lebanon although no human cases have been reported from those countries [177–180].

WNV continued to circulate in northern and sub-Saharan Africa throughout the late 20th and early 21st century, causing outbreaks in Algeria, Morocco, Tunisia, the Democratic Republic of the Congo, and South Africa, along with sporadic cases and seropositivity in humans and/or horses distributed throughout the continent [165, 181–184]. Active transmission has continued in northern Africa, with outbreaks reported in Morocco in 2010 and Tunisia in 2012 and ongoing sporadic transmissions in Egypt and Algeria [165, 183, 185–189].

The regular pattern of infection in South Africa prior to 1974 was sporadic, relatively mild human infections and epizootics, with epidemics in humans occurring in 1974 and 1984 (reviewed in [8]). The relative nonpathogenicity of human and equine infections in South Africa had been attributed to reduced pathogenicity of lineage 2 WNV strains; however, later reports of WNND caused by lineage 2 WNV infections in South Africa suggested that the full clinical extent of WNV infection in earlier epidemics may not have been recognized [79, 156]. In 2010, the first case of lineage 1 WNV occurring in South Africa caused the death of a pregnant mare [190]. Infections caused by lineage 2 in Madagascar have also generally been considered mild to inapparent; one fatal case of WNND originated in Madagascar in 2011, although it was speculated that the patient had a deficient antibody response [191].

Recent reports have indicated ongoing transmission in other regions of sub-Saharan Africa. Eleven cases of acute febrile illness were caused by WNV in Guinea in 2006 [192]. A 2009 seroprevalence study in Ghana indicated that WNV is endemic, with most WNV cases occurring in childhood [193]. A fatality due to WNND was reported in Gabon in 2009 [194]. A study in Nigeria demonstrated that 25% of tested febrile patients, many of whom were infected with *Plasmodium falciparum* or *Salmonella* Typhi, were seropositive for WNV, suggesting that WNV infection in this region may be mistaken for these diagnoses or for other cocirculating arboviruses [195]. Seroconversion of sentinel chickens was observed in Senegal in 2009 [196]. In eastern Africa, human infections and mosquitoes positive for WNV lineage 2 were reported in Djibouti from 2010–2011 [197]. Recent positivity for WNV in Kenya has also been reported in ticks collected from 2010–2012 and mosquitoes from 2007–2011 [121, 198].

7. WNV in Southern and Eastern Asia, Australia, and Oceania

In the early 1950s and 1960s, seropositivity for WNV was demonstrated throughout India and as far east as Myanmar [199, 200]. Sporadic cases were documented in India throughout the 1970s–2000s [3]. Most sequenced isolates from India separate into a distinct lineage referred to as lineage 5 or lineage 1C, although lineage 1A isolates have also been reported [3, 72, 86, 201]. Although WNV had previously been shown to cause neurological disease, the first pediatric fatalities from WNND were reported in India, where three children died of WNV encephalitis in 1981 [5]. Pediatric WNND cases have been frequently reported in Indian WNV outbreaks, in contrast to North American and European WNV outbreaks, in which pediatric cases are relatively infrequent [3, 5, 202–204].

Recent reports on WNV in India have included ongoing isolation and sequencing of both WNV lineages 1A and 5, as well as cocirculation and possibly coinfection with JEV in 2006 in areas of northeastern India where both WNV and JEV are endemic [86, 201, 202, 204, 205]. The 2010 outbreak of lineage 1 WNV in Tamil Nadu state was associated with ocular disease, an infrequently reported WNV complication [201].

The recent lineage 5 isolates reported from northeastern India were more neuroinvasive and pathogenic in mice than Indian isolates from 1982 and earlier [86]. Cases of WNND have also been reported from Pakistan along with human seroprevalences ranging from 12 to 54% [206–209].

Isolations of WNV have been reported in Malaysia and Cambodia, and seropositivity for WNV was also noted in Myanmar, Thailand, and the Philippines [88, 200, 210–212]. Lineage 2 WNV was sequenced from an acute febrile specimen collected in 2004 in Indonesia [81]. Recently, WNV has also been isolated from clinical specimens collected in Nepal from 2009–2010; sequenced fragments of both isolates showed homology primarily to lineage 1 viruses, but one fragment of each was more similar to lineage 2 than to lineage 1 [213].

In China, seropositivity for WNV was first reported in birds from Yunnan province in 1988 [214, 215]. The first confirmed human cases of WNV in China were reported in 2013 but occurred during a 2004 outbreak of fever and neurological disease in Xinjiang province in northwestern China, in which diagnosis was delayed due to antibody cross-reactivity with Japanese encephalitis virus [214]. Seropositivity for WNV in Shanghai was reported in 14.9% of cats and 4.9% of dogs tested in 2010, as well as in captive resident birds from 2009–2010, but no human cases have been reported from southern or eastern China [216, 217]. In South Korea, antibody against WNV was detected in 5/1531 bird specimens in a 2009 study, but no resident birds were seropositive [218].

Kunjin virus, which was originally considered to be a closely related virus but is now considered a subspecies of WNV lineage I, was first isolated in Australia in 1960 [219, 220]. Symptoms of WNV/Kunjin in Australia are considered relatively mild, with infrequent WNND and no deaths reported [115, 221]. WNV/Kunjin has continued to cause intermittent cases of equine and human disease in Australia, primarily in the northwest, where it frequently cocirculates with the related flavivirus Murray Valley encephalitis virus (MVEV) [221]. In 2011, an outbreak of WNV (co-circulating with MVEV) in horses in southeastern Australia was attributed to a strain of WNV designated WNV_{NSW2011}, which was closely related to Kunjin virus, but carried two amino acid changes previously associated with increased virulence in North American WNV NY99 strains [222–224]. These changes rendered WNV_{NSW2011} significantly more neuroinvasive than previously observed Australian strains. However, no human cases were reported from this outbreak, and a serosurvey in Victoria showed little evidence of recent human WNV infection [225].

8. WNV in Europe

The presence of WNV was first discovered in Europe in 1958 in Albania with detection of neutralizing antibodies in human sera [226, 227]. The first documented outbreak of WNV occurred in southern France in 1962–1963, causing WNND in both humans and horses [1, 9]. Following that outbreak, no further WNND cases in humans were reported until 1985, although virus activity in the region has been

confirmed on multiple occasions. The virus was isolated from mosquitoes in Portugal and the Czech Republic, migrating birds in Slovakia, and western Ukraine, and ticks in Hungary and the Moldavia region [227–231]. WNV was also sporadically detected in serological surveys of humans, migratory birds, and domestic animals in the countries throughout southern and eastern Europe and the Mediterranean basin, although the virus was not considered a public health concern during that time due to the absence of reported WNND [227, 232, 233].

However, the situation has changed dramatically in the last three decades with a series of symptomatic WNV outbreaks in several European countries. Human WNND cases were first observed in western Ukraine in 1985, followed by a period of relative silence and two major epidemics: in Romania in 1996 and in Russia in 1999 [14, 15, 232]. During the outbreak in Romania, 835 patients were hospitalized with neurological symptoms and 343 were confirmed to be WNV-positive. The epidemic caused 17 deaths [15]. The mortality rate was even higher in Russia: out of 826 patients who presented with symptoms, 183 tested positive in serological essays, and 40 died of acute aseptic meningoencephalitis [14].

Other notable outbreaks with human cases from 2000–2009 include the reemergence of WNV in France in 2000–2003, Italy in 2008–2009, and Hungary in 2008 [232, 234, 235]. In France in 2000, WNND cases were confirmed in 76 horses, and 21 of them died; interestingly, the same region of the country was affected as in the outbreak of 1962 [236]. WNND cases described in 2003 involved horses and humans [237]. A subsequent serologic survey in horses suggested the possibility of persistent WNV circulation in the area [238]. The 2008 outbreak in Italy was preceded by a 1998 event with 14 encephalitic equine cases and 4 asymptomatic cases in humans; a retrospective study revealed a 38% seroprevalence rate in horses in the region [239, 240]. In 2008–2009, both equine and human WNND cases were reported [241]. In Hungary, the sudden spread of the virus in 2008 caused 12 equine and 22 human neuroinvasive cases [234]. Following the large outbreak in 1999, Russia experienced annual summer transmissions with sporadic outbreaks primarily in the south [242]. The three most affected regions were Astrakhan, Rostov, and Volgograd provinces with outbreaks in 2007, 2010, and 2012, although recently the range of the virus has apparently expanded, with cases reported further north- and eastward in several provinces including southern parts of Siberia [166].

With the outbreaks becoming more frequent and sporadic cases surfacing all over Europe, enhanced surveillance programs were established in many European countries [232, 243]. One such program was instrumental in promptly identifying WNV cases during the largest recorded outbreak in Italy in 2012, where simultaneous circulation of both WNV lineage 1 and lineage 2 was documented [244–247]. From 2010–2013, human WNV cases were reported in Austria, Bosnia and Herzegovina, Croatia, Greece, Hungary, Italy, Kosovo, the Former Yugoslav Republic of Macedonia, Montenegro, the Russian Federation, Serbia, Spain, and Ukraine [165, 248–253]. Greece and Russia experienced high WNV activity each year from 2010–2013, and 302 cases were

reported from Serbia in 2013 [165, 166]. Additionally, the presence of WNV was confirmed in the Czech Republic, Portugal, and other countries where it had not previously been identified, with most of the reports suggesting seasonal introduction by multiple routes and continuous low-level WNV circulation in Europe [254, 255].

Notably, prior to 2008, lineage 1 viruses were responsible for severe WNND cases in humans in Europe, and lineage 2 viruses were only reported in sub-Saharan Africa and Madagascar until 2004. However, the cases in Hungary were caused by lineage 2 WNV, with subsequent spread into Austria, Italy, Russia, Greece, Serbia, and Croatia [85, 248, 255–260]. The strain isolated from the 2010 Greek outbreak, WNV Nea-Santa-Greece 2010, was shown to carry a mutation previously associated with increased virulence in corvids in lineage 1 WNV strains [261, 262].

Countries with established surveillance programs and no reported clinical cases so far include the U.K., Germany, and Switzerland [263–265]. One serologic study in the U.K. identified WNV-seropositive wild birds, although subsequent studies have not found evidence of WNV circulation in birds [266–269]. In Germany and Poland, seroprevalence in birds was relatively low [264, 270].

9. WNV in the United States

WNV infection is a major public health concern in the United States, where the virus has become endemic causing recurring outbreaks for 14 consecutive years. The initial outbreak in the U.S. resulted in 62 reported cases, including 59 WNND cases and 7 deaths; however, estimates based on serosurveillance suggest that 2.6% of the population near the outbreak epicenter in New York City was affected in that outbreak [133]. The WNV strain associated with the U.S. outbreak, designated WNV NY99, was a lineage 1 strain closely related to an isolate from the outbreak in Israel in 1998, and both the U.S. and Israeli strains were related to a Tunisian isolate from 1997 [70, 71, 77, 271]. By the summer of 2000, the virus had also caused human disease in the states of New Jersey and Connecticut with a total of 21 cases reported including 19 WNND cases that resulted in 2 deaths [272].

In contrast to the historically observed pattern of outbreaks in Europe and Africa between the 50s and the 90s, in which epidemics were followed by years of inactivity, WNV continued to spread in the U.S. following its introduction. In the summer of 2001, the virus was found in 10 states with 66 total reported cases (64 WNND) and 9 deaths. In 2002, 40 states reported a total of 4,156 WNV human cases to the CDC, with 70.9% (2,946) classified as WNND resulting in 284 fatalities. Possibly due to increased awareness in the medical community through an outreach program by the HHS, in 2003 the total number of reported cases increased 42% to 9,862; however the number of WNND cases declined to 2,866, which represented 29% of reported cases. By 2004, WNV had been detected in all of the contiguous 48 states and was considered endemic. Another large outbreak occurred in 2006, with 177 deaths and 1,495 WNND cases, out of a total of 4,260 cases. Coincident with the 2002–2003 outbreaks,

a new viral genotype known as WN02 replaced the original viral genotype NY99; the new genotype was observed to disseminate more efficiently in North American *Culex pipiens* and *Culex tarsalis* mosquitoes than the NY99 genotype [273–276].

The intensity of WNV activity in the U.S. was very high between 2002 and 2007, with over 1,000 WNND cases per year. A decline in the number of cases began in 2008, and comparatively low activity continued through 2011 when only 712 total WNV cases were reported. In 2012, however, another large outbreak of WNV occurred in the U.S., causing 2,873 WNND cases and the most deaths [277] ever reported in a single WNV season. Activity in the U.S. in 2013 was moderate, with 1,267 WNND cases and 119 deaths in 2013 reported as of May 9, 2014. From 1999–2013, there have been a total of 39,557 reported cases of WNV in the U.S. of which 17,381 were WNND, resulting in 1,667 deaths, an average of 111.1 deaths/year [278] (Figure 5).

Based on epidemiological estimates that for each case of WNND there are 150 to 350 human infections, 2.6 to 6.1 million people in the United States have been infected with WNV over the past 14 years. Through 2010, it was estimated that 1.1% of the U.S. population had been infected by WNV, with the highest incidence in the state of South Dakota (13.3%) [123, 279]. Because most WNV infections are asymptomatic or mild, many human infections may not be recognized, and there may be significant underreporting of milder symptomatic cases [133, 279].

10. WNV in Other Parts of North America

In 2001, WNV was first detected in 128 dead birds and 9 mosquito pools in Ontario, Canada [280]. Human cases in Canada were first reported in 2002, with 394 in Ontario and 20 in Quebec [281]. In 2003, WNV spread westward to Manitoba, Saskatchewan, and Alberta, but did not reach British Columbia until 2009 [281, 282]. Since 2002, Canada has experienced annual summer outbreaks similar to those in the United States, with the largest outbreaks occurring in 2003 (1,481 cases), 2007 (2,215 cases), and 2012 (428 cases) [281, 283] (Figure 6).

The first WNV activity in the Caribbean was a human WNV encephalitis case reported at the end of 2001 in the Cayman Islands [284]. Most Caribbean WNV activity for the next few years was limited to observations of seropositivity in birds and horses. In 2002, WNV activity was observed in migratory and resident birds in Jamaica and the Dominican Republic, and in horses in Guadeloupe. An avian serosurvey in Jamaica, Puerto Rico, and Mexico in spring 2002 reported detection of specific neutralizing antibodies for WNV in 11 resident species from Jamaica only [285]. In the Dominican Republic, a seroepidemiological study performed in birds sampled in November 2002 on the eastern side of the country showed anti-WNV antibodies in 15% (5/33) of resident birds [286]. By 2003, WNV seropositivity had also been detected in resident birds on the northwestern side of the Dominican Republic [277]. A serosurvey of 360 healthy horses in Guadeloupe showed an increase in prevalence of IgG antibodies to WNV

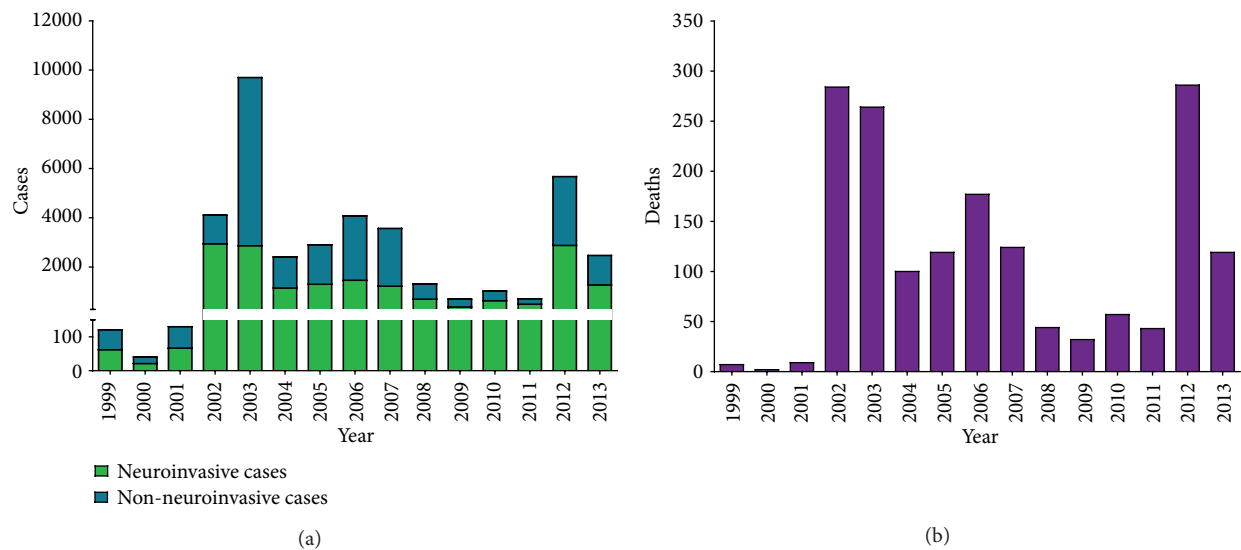


FIGURE 5: (a) Neuroinvasive and nonneuroinvasive cases of WNV in the United States reported to the CDC, 1999–2013. (b) Deaths from WNV infection in the United States reported to the CDC, 1999–2013.

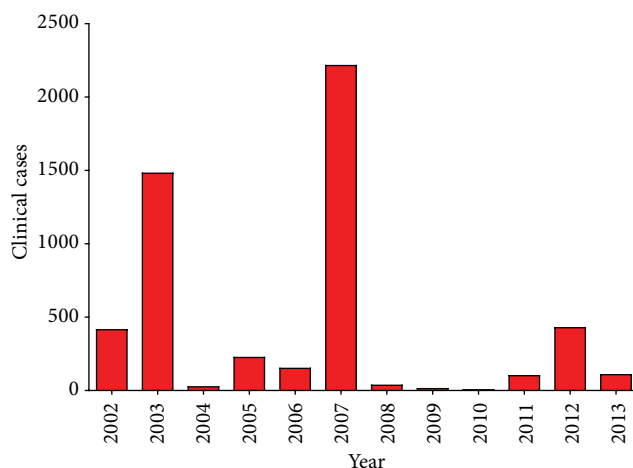


FIGURE 6: Total clinical WNV cases in Canada reported to the Public Health Agency of Canada, 2002–2013.

from 8.8% in June 2002 to 50% in January 2003, indicating a high incidence of WNV infections in horses within that 6-month period [287].

The second Caribbean human WNV encephalitis case occurred in the Bahamas in July 2003 [288]. WNV was detected in Trinidad in October, 2004, in a serosurvey of 60 horses and 40 birds, with reported seropositivity of 3% and 5%, respectively [288, 289]. In Cuba, WNV infection was confirmed by serologic assays in 4 asymptomatic horses and 3 humans with encephalitis in 2003 and 2004 [290]. A 2004 serosurvey of over 1900 resident and migrant birds in Puerto Rico and Cuba found 10 WNV-positive birds (9 migrant, 1 resident) in Puerto Rico and 3 birds (1 migrant, 2 resident) in Cuba [291]. Three seropositive horses were observed in 2004–2005 in Puerto Rico, followed by detection of WNV in

three blood donors in 2007 [292]. A 2007 isolate from Puerto Rico carried the mutation V159A in the envelope gene, which is characteristic of the WN02 genotype which replaced the original NY99 genotype in the U.S. [293]. Two further WNV human cases were detected in Haiti during surveillance of febrile patients following Hurricane Jeanne in 2004 [294].

In 2002, WNV appeared in Mexico, with reports of encephalitis-like illness in horses in different areas, concurrent with reports of WNV encephalitis outbreaks in horses along the Texas border in the states of Coahuila, Tamaulipas, and Chihuahua [295]. Mexico has reported low numbers of cases in humans, horses, and birds, primarily from the northern border with the United States. The first confirmed autochthonous human case of WNV in Mexico was reported in 2004 [296]. A fatal human case in 2009 was reported in a 40-year-old man who had mild symptoms for several weeks then progressed to neurological disease, coma, and death [297].

A surveillance study in Mexico found relatively low levels of WNV transmission and disease, which were attributed to multiple factors including the interactions of amplifying hosts, vectors, and circulating virus strains, in combination with climate, habitat, and circulation of interfering flaviviruses [298]. A Mexican isolate from 2003 was shown to have reduced pathogenicity for mice, crows, and sparrows, which may also have contributed to a reduced presence of WNV in Mexico [299, 300].

In El Salvador, an investigation of outbreaks from 2003 revealed that 25% (18/73) of equine specimens tested had antibodies to WNV and were confirmed by plaque reduction neutralization tests (PRNT) [301]. In October 2003, WNV was also identified in horses in Belize [289].

A 2003–2004 serosurvey conducted at multiple locations in Guatemala detected 9 horses positive for WNV [302]. Seropositivity in horses in Costa Rica was also reported from

a 2004 serosurvey [303]. The only human case of WNV from Nicaragua was reported in a Spanish missionary who became ill in the summer of 2006 while living in Nicaragua and was subsequently transferred to Spain for treatment, where he was diagnosed [18].

11. WNV in South America

The first detection of WNV in South America was in an autumn 2004 epidemiological survey of horses which had not been vaccinated against WNV or traveled outside of Córdoba and Sucre in the Caribbean region of Colombia [304, 305].

WNV was next reported in northern Argentina, where WNV was isolated from the brains of 3 horses that died from encephalitis in February 2006 [306]. A later report showed that resident birds in Córdoba, Chaco, and Tucumán provinces had antibodies to WNV as early as January 2005, and seroconversions were observed in three birds between January and March 2005 [307]. In December 2006, health authorities reported 4 human cases, 1 case in the city of Marcos Juárez in Córdoba province and 3 additional cases in Chaco province [17]. The case in Córdoba occurred in March of that year in a 58-year-old man who had not traveled outside the country in recent years, suggesting that the disease was contracted locally [17].

In 2006, WNV was also reported in birds and horses in Venezuela, in a seroepidemiological study with PRNT confirmation [308]. WNV was detected in Brazil in a study performed on samples collected in 2009 from mosquitoes, horses, and caimans from the Pantanal region of Central-West Brazil, in which a total of 5 out of 168 horse specimens tested positive for WNV, using a flavivirus-specific epitope-blocking enzyme-linked immunosorbent assay with confirmation of reactive specimens by PRNT [309]. Further studies performed with specimens from the Pantanal region, where WNV cocirculates with multiple other flaviviruses, have found WNV seropositivity confirmed by PRNT in horse and chicken samples collected in 2009 and later [310–312]. WNV seropositivity was also reported in an equine sample collected in 2009 in Paraíba state in northeastern Brazil [313]. However, WNV has not yet been associated with human or equine illness in Brazil [314].

A study conducted on a subset of 20,880 samples from individuals with acute febrile illnesses from Bolivia, Paraguay, Ecuador, and Peru from 2000–2007 identified at least one patient with PRNT-confirmed seropositivity for WNV; however, no virus was isolated, and the number and location of WNV-positive patients were not given [315]. A 2011 serosurvey of horses in Bolivia found PRNT-confirmed seropositivity for WNV, although no horses were IgM-positive, indicating that WNV had circulated in the area prior to 2011 [316].

Interestingly, sequences obtained from Colombian viral isolates in 2008 were most closely related to 2001 Louisiana, U.S. sequences of the NY99 genotype, suggesting that the WN02 genotype which replaced NY99 in the U.S. had not progressed southward over that time period [317].

12. Conclusion

Since its discovery in 1937, West Nile virus has spread beyond its original known geographic range and caused human disease on every continent except Antarctica. It is now the most widespread cause of arboviral neurological disease in the world. With no vaccine available to date and limited treatment options, transmission via organ donation and blood transfusion also poses a risk.

While expansion of WNV into Central America, South America, and the Caribbean has been marked by relatively few human WNND cases and recovery of attenuated viruses, characterization of strains isolated from recent outbreaks in Greece, Australia, and India shows increased virulence in tissue culture and/or animal models [86, 222, 262, 300]. However, none of the observed changes has been directly correlated to virulence in human infections.

Recent large outbreaks of human WNND in Europe and North America, as well as ongoing transmission in the Middle East, Africa, and Asia, illustrate the need for continued surveillance and preventative measures. The risk for transmission and outbreaks remains high in the many parts of the world with suitable mosquito vectors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] G. Balanca, N. Gaidet, G. Savini et al., "Low West Nile virus circulation in wild birds in an area of recurring outbreaks in Southern France," *Vector-Borne and Zoonotic Diseases*, vol. 9, no. 6, pp. 737–741, 2009.
- [2] H. Bernkopf, S. Levine, and R. Nerson, "Isolation of West Nile virus in Israel," *The Journal of Infectious Diseases*, vol. 93, no. 3, pp. 207–218, 1953.
- [3] V. P. Bondre, R. S. Jadhav, A. C. Mishra, P. N. Yergolkar, and V. A. Arankalle, "West Nile virus isolates from India: evidence for a distinct genetic lineage," *Journal of General Virology*, vol. 88, no. 3, pp. 875–884, 2007.
- [4] E. Flatau, D. Kohn, O. Daher, and N. Varsano, "West Nile fever encephalitis," *Israel Journal of Medical Sciences*, vol. 17, no. 11, pp. 1057–1059, 1981.
- [5] S. George, M. Gourie-Devi, J. A. Rao, S. R. Prasad, and K. M. Pavri, "Isolation of West Nile virus from the brains of children who had died of encephalitis," *Bulletin of the World Health Organization*, vol. 62, no. 6, pp. 879–882, 1984.
- [6] N. Goldblum, V. V. Sterk, and B. Paderski, "West Nile fever: The clinical features of the disease and the isolation of West Nile virus from the blood of nine human cases," *The American Journal of Epidemiology*, vol. 59, no. 1, pp. 89–103, 1954.
- [7] K. Marberg, N. Goldblum, V. V. Sterk, W. Jasinska-Klingberg, and M. A. Klingberg, "The natural history of West Nile fever I. Clinical observations during an epidemic in Israel," *The American Journal of Epidemiology*, vol. 64, no. 3, pp. 259–269, 1956.

- [8] P. G. Jupp, "The ecology of West Nile virus in South Africa and the occurrence of outbreaks in humans," *Annals of the New York Academy of Sciences*, vol. 951, pp. 143–152, 2001.
- [9] B. Murgue, S. Murri, H. Triki, V. Deubel, and H. G. Zeller, "West Nile in the Mediterranean basin: 1950–2000," *Annals of the New York Academy of Sciences*, vol. 951, pp. 117–126, 2001.
- [10] K. C. Smithburn, T. P. Hughes, A. W. Burke, and J. H. Hall, "A neurotropic virus isolated from the blood of a native of Uganda," *The American Journal of Tropical Medicine and Hygiene*, vol. 20, pp. 471–472, 1940.
- [11] I. Spigland, W. Jasinska-Klingberg, E. Hofshi, and N. Goldblum, "Clinical and laboratory observations in an outbreak of West Nile fever in Israel in 1957," *Harefuah*, vol. 54, no. 11, pp. 275–280, 1958.
- [12] W. Pruzanski and R. Altman, "Encephalitis due to West Nile fever virus," *World neurology*, vol. 3, pp. 524–528, 1962.
- [13] D. E. Carey, F. M. Rodrigues, R. M. Myers, and J. K. Webb, "Arthropod-borne viral infections in children in Vellore, South India, with particular reference to dengue and West Nile viruses," *Indian Pediatrics*, vol. 5, no. 7, pp. 285–296, 1968.
- [14] A. E. Platonov, G. A. Shipulin, O. Y. Shipulina et al., "Outbreak of West Nile virus infection, Volgograd Region, Russia, 1999," *Emerging Infectious Diseases*, vol. 7, no. 1, pp. 128–132, 2001.
- [15] T. F. Tsai, F. Popovici, C. Cernescu, G. L. Campbell, and N. I. Nedelcu, "West Nile encephalitis epidemic in Southeastern Romania," *The Lancet*, vol. 352, no. 9130, pp. 767–771, 1998.
- [16] M. Weinberger, S. D. Pitlik, D. Gandacu et al., "West Nile fever outbreak, Israel, 2000: epidemiologic aspects," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 686–691, 2001.
- [17] ISID, "West Nile Virus Update 2006—Western Hemisphere (23): Argentina: First Case," 2006, <http://www.promedmail.org/direct.php?id=20061228.3642>.
- [18] B. M. Maillou, R. López-Vélez, F. Norman, F. de Ory, M. P. Sanchez-Seco, and C. G. Fedele, "Importation of West Nile virus infection from Nicaragua to Spain," *Emerging Infectious Diseases*, vol. 14, no. 7, pp. 1171–1173, 2008.
- [19] C. H. Calisher, N. Karabatsos, J. M. Dalrymple et al., "Antigenic relationships between flaviviruses as determined by cross-neutralization tests with polyclonal antisera," *Journal of General Virology*, vol. 70, no. 1, pp. 37–43, 1989.
- [20] A. T. de Madrid and J. S. Porterfield, "The flaviviruses (group B arboviruses): a cross neutralization study," *Journal of General Virology*, vol. 23, no. 1, pp. 91–96, 1974.
- [21] E. Castle, T. Nowak, U. Leidner, and G. Wengler, "Sequence analysis of the viral core protein and the membrane-associated proteins V1 and NV2 of the flavivirus West Nile virus and of the genome sequence for these proteins," *Virology*, vol. 145, no. 2, pp. 227–236, 1985.
- [22] E. Castle, U. Leidner, T. Nowak, G. Wengler, and G. Wengler, "Primary structure of the West Nile flavivirus genome region coding for all nonstructural proteins," *Virology*, vol. 149, no. 1, pp. 10–26, 1986.
- [23] G. Coia, M. D. Parker, G. Speight, M. E. Byrne, and E. G. Westaway, "Nucleotide and complete amino acid sequences of Kunjin virus: Definitive gene order and characteristics of the virus-specified proteins," *Journal of General Virology*, vol. 69, no. 1, pp. 1–21, 1988.
- [24] G. Speight, G. Coia, M. D. Parker, and E. G. Westaway, "Gene mapping and positive identification of the non-structural proteins NS2A, NS2B, NS3, NS4B and NS5 of the flavivirus Kunjin and their cleavage sites," *Journal of General Virology*, vol. 69, no. 1, pp. 23–34, 1988.
- [25] G. Wengler, E. Castle, U. Leidner, T. Nowak, and G. Wengler, "Sequence analysis of the membrane protein V3 of the flavivirus West Nile virus and of its gene," *Virology*, vol. 147, no. 2, pp. 264–274, 1985.
- [26] M. A. Brinton, A. V. Fernandez, and J. H. Disposito, "The 3'-nucleotides of flavivirus genomic RNA form a conserved secondary structure," *Virology*, vol. 153, no. 1, pp. 113–121, 1986.
- [27] G. Wengler and E. Castle, "Analysis of structural properties which possibly are characteristic for the 3'-terminal sequence of the genome RNA of flaviviruses," *Journal of General Virology*, vol. 67, no. 6, pp. 1183–1188, 1986.
- [28] T. Nowak, P. M. Farber, G. Wengler, and G. Wengler, "Analyses of the terminal sequences of West Nile virus structural proteins and of the in vitro translation of these proteins allow the proposal of a complete scheme of the proteolytic cleavages involved in their synthesis," *Virology*, vol. 169, no. 2, pp. 365–376, 1989.
- [29] F. X. Heinz and K. Stiasny, "Flaviviruses and their antigenic structure," *Journal of Clinical Virology*, vol. 55, no. 4, pp. 289–295, 2012.
- [30] A. A. Khromykh and E. G. Westaway, "RNA binding properties of core protein of the flavivirus Kunjin," *Archives of Virology*, vol. 141, no. 3–4, pp. 685–699, 1996.
- [31] L. Markoff, B. Falgout, and A. Chang, "A conserved internal hydrophobic domain mediates the stable membrane integration of the dengue virus capsid protein," *Virology*, vol. 233, no. 1, pp. 105–117, 1997.
- [32] Y. Zhang, J. Corver, P. R. Chipman et al., "Structures of immature flavivirus particles," *The EMBO Journal*, vol. 22, no. 11, pp. 2604–2613, 2003.
- [33] F. Guirakhoo, F. X. Heinz, C. W. Mandl, H. Holzmann, and C. Kunz, "Fusion activity of flaviviruses: comparison of mature and immature (prM-containing) tick-borne encephalitis virions," *Journal of General Virology*, vol. 72, no. 6, pp. 1323–1329, 1991.
- [34] F. X. Heinz, K. Stiasny, G. Puschner-Auer et al., "Structural changes and functional control of the tick-borne encephalitis virus glycoprotein E by the heterodimeric association with protein prM," *Virology*, vol. 198, no. 2, pp. 109–117, 1994.
- [35] K. Stadler, S. L. Allison, J. Schlich, and F. X. Heinz, "Proteolytic activation of tick-borne encephalitis virus by furin," *Journal of Virology*, vol. 71, no. 11, pp. 8475–8481, 1997.
- [36] Y. Zhang, B. Kaufmann, P. R. Chipman, R. J. Kuhn, and M. G. Rossmann, "Structure of immature West Nile virus," *Journal of Virology*, vol. 81, no. 11, pp. 6141–6145, 2007.
- [37] J. Junjhon, T. J. Edwards, U. Utaipat et al., "Influence of prM cleavage on the heterogeneity of extracellular dengue virus particles," *Journal of Virology*, vol. 84, no. 16, pp. 8253–8358, 2010.
- [38] B. Kaufmann and M. G. Rossmann, "Molecular mechanisms involved in the early steps of flavivirus cell entry," *Microbes and Infection*, vol. 13, no. 1, pp. 1–9, 2011.
- [39] J. M. Smit, B. Moesker, I. Rodenhuis-Zybert, and J. Wilschut, "Flavivirus cell entry and membrane fusion," *Viruses*, vol. 3, no. 2, pp. 160–171, 2011.
- [40] K. Stiasny and F. X. Heinz, "Flavivirus membrane fusion," *Journal of General Virology*, vol. 87, no. 10, pp. 2755–2766, 2006.
- [41] A. A. Khromykh, P. L. Sedlak, and E. G. Westaway, "trans-Complementation analysis of the flavivirus Kunjin ns5 gene reveals an essential role for translation of its N-terminal half in RNA replication," *Journal of Virology*, vol. 73, no. 11, pp. 9247–9255, 1999.

- [42] B. D. Lindenbach and C. M. Rice, "trans-complementation of yellow fever virus NS1 reveals a role in early RNA replication," *Journal of Virology*, vol. 71, no. 12, pp. 9608–9617, 1997.
- [43] J. M. Mackenzie, M. K. Jones, and P. R. Young, "Immunolocalization of the dengue virus nonstructural glycoprotein NS1 suggests a role in viral RNA replication," *Virology*, vol. 220, no. 1, pp. 232–240, 1996.
- [44] P. Borowski, A. O. Niebuhr, M. Mueller et al., "Purification and characterization of West Nile virus nucleoside triphosphatase (NTPase)/helicase: evidence for dissociation of the NTPase and helicase activities of the enzyme," *Journal of Virology*, vol. 75, pp. 3220–3229, 2001.
- [45] T. J. Chambers, A. Nestorowicz, S. M. Amberg, and C. M. Rice, "Mutagenesis of the yellow fever virus NS2B protein: effects on proteolytic processing, NS2B-NS3 complex formation, and viral replication," *Journal of Virology*, vol. 67, no. 11, pp. 6797–6807, 1993.
- [46] B. Falgout, R. H. Miller, and C.-J. Lai, "Deletion analysis of dengue virus type 4 nonstructural protein NS2B: identification of a domain required for NS2B-NS3 protease activity," *Journal of Virology*, vol. 67, no. 4, pp. 2034–2042, 1993.
- [47] A. E. Gorbalenya, E. V. Koonin, A. P. Donchenko, and V. M. Blinov, "Two related superfamilies of putative helicases involved in replication, recombination, repair and expression of DNA and RNA genomes," *Nucleic Acids Research*, vol. 17, no. 12, pp. 4713–4730, 1989.
- [48] S. A. Shiryayev, A. V. Chernov, A. E. Aleshin, T. N. Shiryayeva, and A. Y. Strongin, "NS4A regulates the ATPase activity of the NS3 helicase: a novel cofactor role of the non-structural protein NS4A from West Nile virus," *Journal of General Virology*, vol. 90, no. 9, pp. 2081–2085, 2009.
- [49] G. Wengler, G. Czaya, P. M. Farber, and J. H. Hegemann, "In vitro synthesis of West Nile virus proteins indicates that the amino-terminal segment of the NS3 protein contains the active centre of the protease which cleaves the viral polyprotein after multiple basic amino acids," *Journal of General Virology*, vol. 72, no. 4, pp. 851–858, 1991.
- [50] A. A. Khromykh, M. T. Kenney, and E. G. Westaway, "trans-Complementation of flavivirus RNA polymerase gene NS5 by using Kunjin virus replicon-expressing BHK cells," *Journal of Virology*, vol. 72, no. 9, pp. 7270–7279, 1998.
- [51] E. V. Koonin, "Computer-assisted identification of a putative methyltransferase domain in NS5 protein of flaviviruses and $\lambda 2$ protein of reovirus," *Journal of General Virology*, vol. 74, no. 4, pp. 733–740, 1993.
- [52] D. Ray, A. Shah, M. Tilgner et al., "West Nile virus 5'-cap structure is formed by sequential guanine N-7 and ribose 2'-O methylations by nonstructural protein 5," *Journal of Virology*, vol. 80, no. 17, pp. 8362–8370, 2006.
- [53] S. Steffens, H.-J. Thiel, and S.-E. Behrens, "The RNA-dependent RNA polymerases of different members of the family Flaviviridae exhibit similar properties in vitro," *Journal of General Virology*, vol. 80, no. 10, pp. 2583–2590, 1999.
- [54] M. A. Brinton, "The molecular biology of West Nile virus: a new invader of the Western hemisphere," *Annual Review of Microbiology*, vol. 56, pp. 371–402, 2002.
- [55] J. Y. Leung, G. P. Pijlman, N. Kondratieva, J. Hyde, J. M. Mackenzie, and A. A. Khromykh, "Role of nonstructural protein NS2A in flavivirus assembly," *Journal of Virology*, vol. 82, no. 10, pp. 4731–4741, 2008.
- [56] W. J. Liu, H. B. Chen, and A. A. Khromykh, "Molecular and functional analyses of Kunjin virus infectious cDNA clones demonstrate the essential roles for NS2A in virus assembly and for a nonconservative residue in NS3 in RNA replication," *Journal of Virology*, vol. 77, no. 14, pp. 7804–7813, 2003.
- [57] S. Youn, R. L. Ambrose, J. M. MacKenzie, and M. S. Diamond, "Non-structural protein-1 is required for West Nile virus replication complex formation and viral RNA synthesis," *Virology Journal*, vol. 10, article 339, 2013.
- [58] P. Avirutnan, A. Fuchs, R. E. Hauhart et al., "Antagonism of the complement component C4 by flavivirus nonstructural protein NS1," *Journal of Experimental Medicine*, vol. 207, no. 4, pp. 793–806, 2010.
- [59] P. Avirutnan, R. E. Hauhart, P. Somnuk, A. M. Blom, M. S. Diamond, and J. P. Atkinson, "Binding of flavivirus nonstructural protein NS1 to C4b binding protein modulates complement activation," *Journal of Immunology*, vol. 187, no. 1, pp. 424–433, 2011.
- [60] K. M. Chung, M. K. Liszewski, G. Nybakken et al., "West Nile virus nonstructural protein NS1 inhibits complement activation by binding the regulatory protein factor H," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 50, pp. 19111–19116, 2006.
- [61] M. C. Kyung, B. S. Thompson, D. H. Fremont, and M. S. Diamond, "Antibody recognition of cell surface-associated NS1 triggers Fc- γ receptor-mediated phagocytosis and clearance of West Nile virus-infected cells," *Journal of Virology*, vol. 81, no. 17, pp. 9551–9555, 2007.
- [62] M. Laurent-Rolle, E. F. Boer, K. J. Lubick et al., "The NS5 protein of the virulent West Nile virus NY99 strain is a potent antagonist of type I interferon-mediated JAK-STAT signaling," *Journal of Virology*, vol. 84, no. 7, pp. 3503–3515, 2010.
- [63] J. L. Wen, B. C. Hua, J. W. Xiang, H. Huang, and A. A. Khromykh, "Analysis of adaptive mutations in Kunjin virus replicon RNA reveals a novel role for the flavivirus nonstructural protein NS2A in inhibition of beta interferon promoter-driven transcription," *Journal of Virology*, vol. 78, no. 22, pp. 12225–12235, 2004.
- [64] W. J. Liu, X. J. Wang, V. V. Mokhonov, P.-Y. Shi, R. Randall, and A. A. Khromykh, "Inhibition of interferon signaling by the New York 99 strain and Kunjin subtype of West Nile virus involves blockage of STAT1 and STAT2 activation by nonstructural proteins," *Journal of Virology*, vol. 79, no. 3, pp. 1934–1942, 2005.
- [65] E. B. Melian, J. H. Edmonds, T. K. Nagasaki, E. Hinzman, N. Floden, and A. A. Khromykh, "West Nile virus NS2A protein facilitates virus-induced apoptosis independently of interferon response," *Journal of General Virology*, vol. 94, no. 2, pp. 308–313, 2013.
- [66] J. L. Muñoz-Jordán, M. Laurent-Rolle, J. Ashour et al., "Inhibition of alpha/beta interferon signaling by the NS4B protein of flaviviruses," *Journal of Virology*, vol. 79, no. 13, pp. 8004–8013, 2005.
- [67] J. R. Wilson, P. F. De Sessions, M. A. Leon, and F. Scholle, "West Nile virus nonstructural protein 1 inhibits TLR3 signal transduction," *Journal of Virology*, vol. 82, no. 17, pp. 8262–8271, 2008.
- [68] T. Bakonyi, Z. Hubálek, I. Rudolf, and N. Nowotny, "Novel flavivirus or new lineage of West Nile virus, Central Europe," *Emerging Infectious Diseases*, vol. 11, no. 2, pp. 225–231, 2005.
- [69] F.-X. Berthet, H. G. Zeller, M.-T. Drouet, J. Rauzier, J.-P. Digoutte, and V. Deubel, "Extensive nucleotide changes and deletions within the envelope glycoprotein genes of Euro-African West Nile viruses," *Journal of General Virology*, vol. 78, no. 9, pp. 2293–2297, 1997.

- [70] X.-Y. Jia, T. Briese, I. Jordan et al., "Genetic analysis of West Nile New York 1999 encephalitis virus," *The Lancet*, vol. 354, no. 9194, pp. 1971–1972, 1999.
- [71] R. S. Lanciotti, G. D. Ebel, V. Deubel et al., "Complete genome sequences and phylogenetic analysis of West Nile virus strains isolated from the United States, Europe, and the Middle East," *Virology*, vol. 298, no. 1, pp. 96–105, 2002.
- [72] F. J. May, C. T. Davis, R. B. Tesh, and A. D. T. Barrett, "Phylogeography of West Nile virus: from the cradle of evolution in Africa to Eurasia, Australia, and the Americas," *Journal of Virology*, vol. 85, no. 6, pp. 2964–2974, 2011.
- [73] J. H. Scherret, M. Poidinger, J. S. Mackenzie et al., "The relationships between West Nile and Kunjin viruses," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 697–705, 2001.
- [74] E. M. Botha, W. Markotter, M. Wolfaardt et al., "Genetic determinants of virulence in pathogenic lineage 2 West Nile virus strains," *Emerging Infectious Diseases*, vol. 14, no. 2, pp. 222–230, 2008.
- [75] A. Vázquez, M. P. Sánchez-Seco, S. Ruiz et al., "Putative new lineage of West Nile virus, Spain," *Emerging Infectious Diseases*, vol. 16, no. 3, pp. 549–552, 2010.
- [76] R. G. McLean, S. R. Ubico, D. Bourne, and N. Komar, "West Nile virus in livestock and wildlife," *Current Topics in Microbiology and Immunology*, vol. 267, pp. 271–308, 2002.
- [77] L. R. Petersen and J. T. Roehrig, "West Nile virus: a reemerging global pathogen," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 611–614, 2001.
- [78] G. Zehender, E. Ebraniati, F. Bernini et al., "Phylogeography and epidemiological history of West Nile virus genotype 1a in Europe and the Mediterranean basin," *Infection, Genetics and Evolution*, vol. 11, no. 3, pp. 646–653, 2011.
- [79] F. J. Burt, A. A. Grobelaar, P. A. Leman, F. S. Anthony, G. V. F. Gibson, and R. Swanepoel, "Phylogenetic relationships of Southern African West Nile virus isolates," *Emerging Infectious Diseases*, vol. 8, no. 8, pp. 820–826, 2002.
- [80] K. Erdélyi, K. Ursu, E. Ferenczi et al., "Clinical and pathologic features of lineage 2 West Nile virus infections in birds of prey in Hungary," *Vector-Borne and Zoonotic Diseases*, vol. 7, no. 2, pp. 181–188, 2007.
- [81] K. S. A. Myint, H. Kosasih, I. M. Artika et al., "Short report: west nile virus documented in Indonesia from acute febrile illness specimens," *The American Journal of Tropical Medicine and Hygiene*, vol. 90, no. 2, pp. 260–262, 2014.
- [82] M. Ciccozzi, S. Peletto, E. Cella et al., "Epidemiological history and phylogeography of West Nile virus lineage 2," *Infection, Genetics and Evolution*, vol. 17, pp. 46–50, 2013.
- [83] M. T. Aliota, S. A. Jones, A. P. Dupuis II, A. T. Ciota, Z. Hubalek, and L. D. Kramer, "Characterization of Rabensburg virus, a flavivirus closely related to West Nile virus of the Japanese encephalitis antigenic group," *PLoS ONE*, vol. 7, no. 6, Article ID e39387, 2012.
- [84] D. K. Lvov, A. M. Butenko, V. L. Gromashevsky et al., "West Nile virus and other zoonotic viruses in Russia: examples of emerging-reemerging situations," *Archives of Virology, Supplement*, no. 18, pp. 85–96, 2004.
- [85] A. E. Platonov, L. S. Karan, T. A. Shopenskaia et al., "Genotyping of West Nile fever virus strains circulating in southern Russia as an epidemiological investigation method: principles and results," *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii*, no. 2, pp. 29–37, 2011.
- [86] P. Chowdhury, S. A. Khan, P. Dutta, R. Topno, and J. Mahanta, "Characterization of West Nile virus (WNV) isolates from Assam, India: insights into the circulating WNV in North-eastern India," *Comparative Immunology, Microbiology and Infectious Diseases*, vol. 37, no. 1, pp. 39–47, 2014.
- [87] G. Fall, M. Diallo, C. Loucoubar, O. Faye, and A. A. Sall, "Vector competence of *Culex neavei* and *Culex quinquefasciatus* (Diptera: Culicidae) from Senegal for lineages 1, 2, Koutango and a putative new lineage of West Nile virus," *American Journal of Tropical Medicine and Hygiene*, vol. 90, no. 4, pp. 747–754, 2014.
- [88] J. S. MacKenzie and D. T. Williams, "The zoonotic flaviviruses of Southern, South-Eastern and Eastern Asia, and Australasia: the potential for emergent viruses," *Zoonoses and Public Health*, vol. 56, no. 6-7, pp. 338–356, 2009.
- [89] K. M. Van Der Meulen, M. B. Pensaert, and H. J. Nauwynck, "West Nile virus in the vertebrate world," *Archives of Virology*, vol. 150, no. 4, pp. 637–657, 2005.
- [90] N. Komar, S. Langevin, S. Hinten et al., "Experimental infection of North American birds with the New York 1999 strain of West Nile virus," *Emerging Infectious Diseases*, vol. 9, no. 3, pp. 311–322, 2003.
- [91] A. M. Kilpatrick, P. Daszak, M. J. Jones, P. P. Marra, and L. D. Kramer, "Host heterogeneity dominates West Nile virus transmission," *Proceedings of the Royal Society B: Biological Sciences*, vol. 273, no. 1599, pp. 2327–2333, 2006.
- [92] A. Gómez, L. D. Kramer, A. P. Dupuis II et al., "Experimental infection of eastern gray squirrels (*Sciurus carolinensis*) with West Nile virus," *The American Journal of Tropical Medicine and Hygiene*, vol. 79, no. 3, pp. 447–451, 2008.
- [93] K. B. Platt, B. J. Tucker, P. G. Halbur et al., "West Nile virus viremia in eastern chipmunks (*Tamias striatus*) sufficient for infecting different mosquitoes," *Emerging Infectious Diseases*, vol. 13, no. 6, pp. 831–837, 2007.
- [94] K. B. Platt, B. J. Tucker, P. G. Halbur et al., "Fox squirrels (*Sciurus niger*) develop West Nile virus viremias sufficient for infecting select mosquito species," *Vector-Borne and Zoonotic Diseases*, vol. 8, no. 2, pp. 225–233, 2008.
- [95] J. J. Root, "West Nile virus associations in wild mammals: a synthesis," *Archives of Virology*, vol. 158, no. 4, pp. 735–752, 2013.
- [96] S. Tiawsirisup, K. B. Platt, B. J. Tucker, and W. A. Rowley, "Eastern cottontail rabbits (*Sylvilagus floridanus*) develop West Nile virus viremias sufficient for infecting select mosquito species," *Vector-Borne and Zoonotic Diseases*, vol. 5, no. 4, pp. 342–350, 2005.
- [97] F. Rodhain, J. J. Petter, R. Albignac, P. Coulanges, and C. Hannoun, "Arboviruses and lemurs in Madagascar: experimental infection of *Lemur fulvus* with yellow fever and West Nile viruses," *The American Journal of Tropical Medicine and Hygiene*, vol. 34, no. 4, pp. 816–822, 1985.
- [98] M. A. Kostiukov, Z. E. Gordeeva, V. P. Bulychev, N. V. Nemova, and O. A. Daniyarov, "The lake frog (*Rana ridibunda*)—one of the food hosts of blood-sucking mosquitoes in Tadzhikistan—a reservoir of the West Nile fever virus," *Meditinskaya Parazitologiya i Parazitarnye Bolezni*, no. 3, pp. 49–50, 1985.
- [99] L. N. Pealer, A. A. Marfin, L. R. Petersen et al., "Transmission of West Nile virus through blood transfusion in the United States in 2002," *The New England Journal of Medicine*, vol. 349, no. 13, pp. 1236–1245, 2003.
- [100] M. Iwamoto, D. B. Jernigan, A. Guasch et al., "Transmission of West Nile virus from an organ donor to four transplant

- recipients," *The New England Journal of Medicine*, vol. 348, no. 22, pp. 2196–2203, 2003.
- [101] "Intrauterine West Nile virus infection—New York, 2002," *Morbidity and Mortality Weekly Report*, vol. 51, no. 50, pp. 1135–1136, 2002.
- [102] A. F. Hinckley, D. R. O'Leary, and E. B. Hayes, "Transmission of West Nile virus through human breast milk seems to be rare," *Pediatrics*, vol. 119, no. 3, pp. e666–e671, 2007.
- [103] Centers for Disease Control and Prevention (CDC), "Possible West Nile virus transmission to an infant through breast-feeding—Michigan," *MMWR Morb Mortal. Wkly Rep*, vol. 51, no. 39, pp. 877–878, 2002.
- [104] Centers for Disease Control and Prevention, "Fatal west nile virus infection after probable transfusion-associated transmission: Colorado," *MMWR: Morbidity and Mortality Weekly Report*, vol. 62, no. 31, p. 622–624, 2013.
- [105] L. R. Petersen and M. P. Busch, "Transfusion-transmitted arboviruses," *Vox Sanguinis*, vol. 98, no. 4, pp. 495–503, 2010.
- [106] S. P. Montgomery, J. A. Brown, M. Kuehnert et al., "Transfusion-associated transmission of West Nile virus, United States 2003 through 2005," *Transfusion*, vol. 46, no. 12, pp. 2038–2046, 2006.
- [107] G. M. Meny, L. Santos-Zabala, A. Szallasi, and S. L. Stramer, "West Nile virus infection transmitted by granulocyte transfusion," *Blood*, vol. 117, no. 21, pp. 5778–5779, 2011.
- [108] Centers for Disease Control and Prevention, "Entomology," 2009, <http://www.cdc.gov/ncidod/dvbid/westnile/mosquito-species.htm>.
- [109] M. J. Turell, D. J. Dohm, M. R. Sardelis, M. L. O'Guinn, T. G. Andreadis, and J. A. Blow, "An update on the potential of North American mosquitoes (Diptera: Culicidae) to transmit West Nile virus," *Journal of Medical Entomology*, vol. 42, no. 1, pp. 57–62, 2005.
- [110] A. M. Kilpatrick, L. D. Kramer, S. R. Campbell, E. O. Alleyne, A. P. Dobson, and P. Daszak, "West Nile virus risk assessment and the bridge vector paradigm," *Emerging Infectious Diseases*, vol. 11, no. 3, pp. 425–429, 2005.
- [111] M. J. Turell, M. R. Sardelis, M. L. O'Guinn, and D. J. Dohm, "Potential vectors of West Nile virus in North America," *Current Topics in Microbiology and Immunology*, vol. 267, pp. 241–252, 2002.
- [112] T. G. Andreadis, "The contribution of culex pipiens complex mosquitoes to transmission and persistence of west nile virus in North America," *Journal of the American Mosquito Control Association*, vol. 28, no. 4, pp. 137–151, 2012.
- [113] T. Balenghien, M. Vazeille, M. Grandadam et al., "Vector competence of some French Culex and Aedes mosquitoes for West Nile virus," *Vector-Borne and Zoonotic Diseases*, vol. 8, no. 5, pp. 589–595, 2008.
- [114] P. G. Jupp, "Laboratory studies on the transmission of West Nile virus by Culex (Culex) univittatus Theobald; factors influencing the transmission rate," *Journal of Medical Entomology*, vol. 11, no. 4, pp. 455–458, 1974.
- [115] J. S. Mackenzie, M. D. Lindsay, R. J. Coelen, A. K. Broom, R. A. Hall, and D. W. Smith, "Arboviruses causing human disease in the Australasian zoogeographic region," *Archives of Virology*, vol. 136, no. 3–4, pp. 447–467, 1994.
- [116] J. Muñoz, S. Ruiz, R. Soriguer et al., "Feeding patterns of potential West Nile virus vectors in South-West Spain," *PLoS ONE*, vol. 7, no. 6, article e39549, 2012.
- [117] M. M. Abbassy, M. Osman, and A. S. Marzouk, "West Nile virus (Flaviviridae: Flavivirus) in experimentally infected Argas ticks (Acari: Argasidae)," *The American Journal of Tropical Medicine and Hygiene*, vol. 48, no. 5, pp. 726–737, 1993.
- [118] P. Formosinho and M. M. Santos-Silva, "Experimental infection of Hyalomma marginatum ticks with West Nile virus," *Acta Virologica*, vol. 50, no. 3, pp. 175–180, 2006.
- [119] H. J. Hutcheson, C. H. Gorham, C. Machain-Williams et al., "Experimental transmission of West Nile virus (Flaviviridae: Flavivirus) by Carios capensis ticks from North America," *Vector-Borne and Zoonotic Diseases*, vol. 5, no. 3, pp. 293–295, 2005.
- [120] C. H. Lawrie, N. Y. Uzcátegui, E. A. Gould, and P. A. Nuttall, "Ixodid and argasid tick species and west nile virus," *Emerging Infectious Diseases*, vol. 10, no. 4, pp. 653–657, 2004.
- [121] O. W. Lwande, J. Lutomia, V. Obanda et al., "Isolation of tick and mosquito-borne arboviruses from ticks sampled from livestock and wild animal hosts in Ijara District, Kenya," *Vector-Borne and Zoonotic Diseases*, vol. 13, no. 9, pp. 637–642, 2013.
- [122] A. V. Bode, J. J. Sejvar, W. J. Pape, G. L. Campbell, and A. A. Marfin, "West Nile Virus disease: a descriptive study of 228 patients hospitalized in a 4-county region of Colorado in 2003," *Clinical Infectious Diseases*, vol. 42, no. 9, pp. 1234–1240, 2006.
- [123] P. J. Carson, S. M. Borchardt, B. Custer et al., "Neuroinvasive disease and west nile virus infection, North Dakota, USA, 1999–2008," *Emerging Infectious Diseases*, vol. 18, no. 4, pp. 684–686, 2012.
- [124] K. Danis, A. Papa, G. Theocharopoulos et al., "Outbreak of West Nile virus infection in Greece, 2010," *Emerging Infectious Diseases*, vol. 17, no. 10, pp. 1868–1872, 2011.
- [125] C. M. Jean, S. Honarmand, J. K. Louie, and C. A. Glaser, "Risk factors for West Nile virus neuroinvasive disease, California, 2005," *Emerging Infectious Diseases*, vol. 13, no. 12, pp. 1918–1920, 2007.
- [126] E. Kopel, Z. Amitai, H. Bin, L. M. Shulman, E. Mendelson, and R. Shefer, "Surveillance of west Nile virus disease, Tel Aviv district, Israel, 2005 to 2010," *Eurosurveillance*, vol. 16, no. 25, 2011.
- [127] N. P. Lindsey, E. B. Hayes, J. E. Staples, and M. Fischer, "West Nile virus disease in children, United States, 1999–2007," *Pediatrics*, vol. 123, no. 6, pp. e1084–e1089, 2009.
- [128] N. P. Lindsey, J. Erin Staples, J. A. Lehman, and M. Fischer, "Surveillance for human west Nile virus disease—United States, 1999–2008," *Morbidity and Mortality Weekly Report*, vol. 59, no. 2, pp. 1–17, 2010.
- [129] N. P. Lindsey, J. E. Staples, J. A. Lehman, and M. Fischer, "Medical risk factors for severe West Nile virus disease, United States, 2008–2010," *The American Journal of Tropical Medicine and Hygiene*, vol. 87, no. 1, pp. 179–184, 2012.
- [130] D. Nash, F. Mostashari, A. Fine et al., "The outbreak of West Nile virus infection in the New York City area in 1999," *The New England Journal of Medicine*, vol. 344, no. 24, pp. 1807–1814, 2001.
- [131] J. L. Patnaik, H. Harmon, and R. L. Vogt, "Follow-up of 2003 human West Nile virus infections, Denver, Colorado," *Emerging Infectious Diseases*, vol. 12, no. 7, pp. 1129–1131, 2006.
- [132] E. B. Hayes and D. R. O'Leary, "West Nile virus infection: a pediatric perspective," *Pediatrics*, vol. 113, no. 5, pp. 1375–1381, 2004.
- [133] F. Mostashari, M. L. Bunning, P. T. Kitsutani et al., "Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey," *The Lancet*, vol. 358, no. 9278, pp. 261–264, 2001.

- [134] S. Zou, G. A. Foster, R. Y. Dodd, L. R. Petersen, and S. L. Stramer, "West Nile fever characteristics among viremic persons identified through blood donor screening," *Journal of Infectious Diseases*, vol. 202, no. 9, pp. 1354–1361, 2010.
- [135] J. D. Fratkin, A. A. Leis, D. S. Stokic, S. A. Slavinski, and R. W. Geiss, "pinal cord neuropathology in human West Nile virus infection," *Archives of Pathology and Laboratory Medicine*, vol. 128, no. 5, pp. 533–537, 2004.
- [136] M. P. Busch, D. J. Wright, B. Custer et al., "West nile virus infections projected from blood donor screening data, United States, 2003," *Emerging Infectious Diseases*, vol. 12, no. 3, pp. 395–402, 2006.
- [137] G. A. F. Ladbury, M. Gavana, K. Danis et al., "Population seroprevalence study after a West Nile virus lineage 2 epidemic, Greece, 2010," *PLoS ONE*, vol. 8, no. 11, Article ID e80432, 2013.
- [138] D. S. Asnis, R. Conetta, G. Waldman, and A. A. Teixeira, "The West Nile virus encephalitis outbreak in the United States (1999–2000): from Flushing, New York, to beyond its borders," *Annals of the New York Academy of Sciences*, vol. 951, pp. 161–171, 2001.
- [139] R. Brilla, M. Block, G. Geremia, and M. Wichter, "Clinical and neuroradiologic features of 39 consecutive cases of West Nile Virus meningoencephalitis," *Journal of the Neurological Sciences*, vol. 220, no. 1-2, pp. 37–40, 2004.
- [140] M. Emig and D. J. Apple, "Severe West Nile virus disease in healthy adults," *Clinical Infectious Diseases*, vol. 38, no. 2, pp. 289–292, 2004.
- [141] A. L. Klee, B. Maldin, B. Edwin et al., "Long-term prognosis for clinical West Nile virus infection," *Emerging Infectious Diseases*, vol. 10, no. 8, pp. 1405–1411, 2004.
- [142] K. O. Murray, S. Baraniuk, M. Resnick et al., "Clinical investigation of hospitalized human cases of West Nile virus infection in Houston, Texas, 2002–2004," *Vector-Borne and Zoonotic Diseases*, vol. 8, no. 2, pp. 167–174, 2008.
- [143] J. J. Sejvar, M. B. Haddad, B. C. Tierney et al., "Neurologic manifestations and outcome of West Nile virus infection," *The Journal of the American Medical Association*, vol. 290, no. 4, pp. 511–515, 2003.
- [144] D. Weiss, D. Carr, J. Kellachan et al., "Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 654–658, 2001.
- [145] C. Klein, I. Kimiagar, L. Pollak et al., "Neurological features of West Nile Virus infection during the 2000 outbreak in a regional hospital in Israel," *Journal of the Neurological Sciences*, vol. 200, no. 1-2, pp. 63–66, 2002.
- [146] C. Pepperell, N. Rau, S. Krajden et al., "West Nile virus infection in 2002: morbidity and mortality among patients admitted to hospital in southcentral Ontario," *Canadian Medical Association Journal*, vol. 168, no. 11, pp. 1399–1405, 2003.
- [147] A. Sribu, C. S. Ceianu, R. I. Panculescu-Gatej et al., "Outbreak of West Nile virus infection in humans, Romania, July to October 2010," *Eurosurveillance*, vol. 16, no. 2, 2011.
- [148] M. Loeb, S. Hanna, L. Nicolle et al., "Prognosis after West Nile virus infection," *Annals of Internal Medicine*, vol. 149, no. 4, pp. 232–241, 2008.
- [149] J. R. Sadek, S. A. Pergam, J. A. Harrington et al., "Persistent neuropsychological impairment associated with West Nile virus infection," *Journal of Clinical and Experimental Neuropsychology*, vol. 32, no. 1, pp. 81–87, 2010.
- [150] R. L. Cook, X. Xu, E. J. Yablonsky et al., "Demographic and clinical factors associated with persistent symptoms after West Nile virus infection," *The American Journal of Tropical Medicine and Hygiene*, vol. 83, no. 5, pp. 1133–1136, 2010.
- [151] M. S. Nolan, A. S. Podoll, A. M. Hause, K. M. Akers, K. W. Finkel, and K. O. Murray, "Prevalence of chronic kidney disease and progression of disease over time among patients enrolled in the Houston west Nile virus cohort," *PLoS ONE*, vol. 7, no. 7, Article ID e40374, 2012.
- [152] T. J. Gray, J. N. Burrow, P. G. Markey et al., "Case report: West nile virus (Kunjin subtype) disease in the Northern Territory of Australia—a case of encephalitis and review of all reported cases," *The American Journal of Tropical Medicine and Hygiene*, vol. 85, no. 5, pp. 952–956, 2011.
- [153] A. R. McMullen, H. Albayrak, F. J. May, C. T. Davis, D. W. C. Beasley, and A. D. T. Barrett, "Molecular evolution of lineage 2 West Nile virus," *Journal of General Virology*, vol. 94, no. 2, pp. 318–325, 2013.
- [154] M. Venter, S. Human, D. Zaayman et al., "Lineage 2 West Nile virus as cause of fatal neurologic disease in horses, South Africa," *Emerging Infectious Diseases*, vol. 15, no. 6, pp. 877–884, 2009.
- [155] M. Venter and R. Swanepoel, "West Nile virus lineage 2 as a cause of zoonotic neurological disease in humans and horses in Southern Africa," *Vector-Borne and Zoonotic Diseases*, vol. 10, no. 7, pp. 659–664, 2010.
- [156] D. Zaayman and M. Venter, "West nile virus neurologic disease in Humans, South Africa, September 2008–May 2009," *Emerging Infectious Diseases*, vol. 18, no. 12, pp. 2051–2054, 2012.
- [157] K. C. Smithburn and R. H. Jacobs, "Neutralization-tests against neurotropic viruses with sera collected in central Africa," *Journal of Immunology*, vol. 44, pp. 9–23, 1942.
- [158] F. N. Macnamara, D. W. Horn, and J. S. Porterfield, "Yellow fever and other arthropod-borne viruses: a consideration of two serological surveys made in South Western Nigeria," *Transactions of the Royal Society of Tropical Medicine & Hygiene*, vol. 53, no. 2, pp. 202–212, 1959.
- [159] R. H. Kokernot, K. C. Smithburn, and M. P. Weinbren, "Neutralizing antibodies to arthropod-borne viruses in human beings and animals in the Union of South Africa," *Journal of Immunology*, vol. 77, no. 5, pp. 313–323, 1956.
- [160] J. L. Melnick, J. R. Paul, J. T. Riordan, V. H. Barnett, N. Goldblum, and E. Zabin, "Isolation from human sera in Egypt of a virus apparently identical to West Nile virus," *Proceedings of the Society for Experimental Biology and Medicine*, vol. 77, no. 4, pp. 661–665, 1951.
- [161] K. C. Smithburn, R. M. Taylor, F. Rizk, and A. Kader, "Immunity to certain arthropod-borne viruses among indigenous residents of Egypt," *The American Journal of Tropical Medicine and Hygiene*, vol. 3, no. 1, pp. 9–18, 1954.
- [162] R. M. Taylor, H. S. Hurlbut, H. R. Dressler, E. W. Spangler, and D. Thrasher, "Isolation of West Nile virus from Culex mosquitoes," *The Journal of the Egyptian Medical Association*, vol. 36, no. 3, pp. 199–208, 1953.
- [163] T. Briese, A. Rambaut, M. Pathmajeyan et al., "Phylogenetic analysis of a human isolate from the 2000 Israel West Nile virus epidemic," *Emerging Infectious Diseases*, vol. 8, no. 5, pp. 528–531, 2002.
- [164] M. Hindiyeh, L. M. Shulman, E. Mendelson, L. Weiss, Z. Grossman, and H. Bin, "Isolation and characterization of West Nile virus from the blood of viremic patients during the 2000

- outbreak in Israel," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 748–750, 2001.
- [165] European Centre for Disease Prevention and Control, "Historical data," 2013, http://ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/Pages/historical-data.aspx.
- [166] European Centre for Disease Prevention and Control, "West Nile fever maps," 2013, http://ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/Pages/index.aspx.
- [167] E. Anis, I. Grotto, E. Mendelson et al., "West Nile fever in Israel: the reemergence of an endemic disease," *Journal of Infection*, vol. 68, no. 2, pp. 170–175, 2014.
- [168] K. Ergunay, N. Ozer, D. Us et al., "Seroprevalence of West Nile virus and tick-borne encephalitis virus in Southeastern Turkey: first evidence for tick-borne encephalitis virus infections," *Vector-Borne and Zoonotic Diseases*, vol. 7, no. 2, pp. 157–161, 2007.
- [169] O. Meço, "West Nile arbovirus antibodies with hemagglutination inhibition (HI) in residents of Southeast Anatolia," *Mikrobiyoloji Bulteni*, vol. 11, no. 1, pp. 3–17, 1977.
- [170] N. Özer, K. Ergünay, F. Simsek et al., "West Nile virus studies in the Sanliurfa Province of Turkey," *Journal of Vector Ecology*, vol. 32, no. 2, pp. 202–206, 2007.
- [171] A. Ozkul, Y. Yildirim, D. Pinar, A. Akcali, V. Yilmaz, and D. Colak, "Serological evidence of West Nile Virus (WNV) in mammalian species in Turkey," *Epidemiology & Infection*, vol. 134, no. 4, pp. 826–829, 2006.
- [172] A. Radda, "Studies on the activity and ecology of arboviruses in Turkey," *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene. Erste Abteilung Originale*, vol. 225, no. 1, pp. 19–26, 1973.
- [173] H. Kalaycioglu, G. Korukluoglu, A. Ozkul et al., "Emergence of West Nile virus infections in humans in Turkey, 2010 to 2011," *Eurosurveillance*, vol. 17, no. 21, 2012.
- [174] K. Naficy and S. Saidi, "Serological survey on viral antibodies in Iran," *Tropical and Geographical Medicine*, vol. 22, no. 2, pp. 183–188, 1970.
- [175] S. Chinikar, A. Javadi, B. Ataei et al., "Detection of West Nile virus genome and specific antibodies in Iranian encephalitis patients," *Epidemiology and Infection*, vol. 140, no. 8, pp. 1525–1529, 2012.
- [176] F. Ahmadnejad, V. Otarod, M. H. Fallah et al., "Spread of West Nile virus in Iran: a cross-sectional serosurvey in equines, 2008–2009," *Epidemiology and Infection*, vol. 139, no. 10, pp. 1587–1593, 2011.
- [177] A. Batieha, E. K. Saliba, R. Graham, E. Mohareb, Y. Hijazi, and P. Wijeyaratne, "Seroprevalence of West Nile, Rift Valley, and sandfly arboviruses in Hashimiah, Jordan," *Emerging Infectious Diseases*, vol. 6, no. 4, pp. 358–362, 2000.
- [178] P. Gallian, P. de Micco, and P. Ghorra, "Seroprevalence of West Nile virus in blood donors at Hôtel Dieu de France, Beirut, Lebanon," *Transfusion*, vol. 50, no. 5, pp. 1156–1158, 2010.
- [179] G. A. Garabedian, R. M. Matossian, and M. N. Musalli, "Serologic evidence of arbovirus infection in Lebanon," *Journal Medical Libanais*, vol. 24, no. 4, pp. 339–350, 1971.
- [180] S. M. Abutarbush and A. M. Al-Majali, "West Nile virus infection in horses in Jordan: clinical cases, seroprevalence and risk factors," *Transboundary and Emerging Diseases*, vol. 61, supplement 1, pp. 1–6, 2014.
- [181] O. Cabre, M. Grandadam, J.-L. Marié et al., "West Nile virus in horses, sub-Saharan Africa," *Emerging Infectious Diseases*, vol. 12, no. 12, pp. 1958–1960, 2006.
- [182] R. C. Kading, E. M. Borland, M. Cranfield, and A. M. Powers, "Prevalence of antibodies to alphaviruses and flaviviruses in free-ranging game animals and nonhuman primates in the greater Congo basin," *Journal of Wildlife Diseases*, vol. 49, no. 3, pp. 587–599, 2013.
- [183] W. Sghaier, O. Bahri, E. Kedous et al., "Retrospective study of viral causes of central nervous system infections in Tunisia (2003–2009)," *Medecine et Sante Tropicales*, vol. 22, no. 4, pp. 373–378, 2012.
- [184] J. C. Morrill, B. K. Johnson, C. Hyams et al., "Serological evidence of arboviral infections among humans of coastal Kenya," *Journal of Tropical Medicine and Hygiene*, vol. 94, no. 3, pp. 166–168, 1991.
- [185] T. B. Hassine, S. Hammami, H. Elghoul, and A. Ghram, "Detection of circulation of West Nile virus in equine in the North-west of Tunisia," *Bulletin de la Societe de Pathologie Exotique*, vol. 104, no. 4, pp. 266–271, 2011.
- [186] H. El Rhaffouli, M. El Harrak, C. Lotfi et al., "Serologic evidence of West Nile Virus infection among humans, Morocco," *Emerging Infectious Diseases*, vol. 18, no. 5, pp. 880–881, 2012.
- [187] H. Fassil, M. El Harrak, and J.-L. Marié, "Epidemiological aspects of west Nile virus infection in Morocco," *Medecine et sante tropicales*, vol. 22, no. 2, pp. 123–125, 2012.
- [188] M. Gabriel, P. Emmerich, C. Frank et al., "Increase in West Nile virus infections imported to Germany in 2012," *Journal of Clinical Virology*, vol. 58, no. 3, pp. 587–589, 2013.
- [189] A. Soliman, E. Mohareb, D. Salman et al., "Studies on West Nile virus infection in Egypt," *Journal of Infection and Public Health*, vol. 3, no. 2, pp. 54–59, 2010.
- [190] M. Venter, S. Human, S. Van Niekerk, J. Williams, C. van Eeden, and F. Freeman, "Fatal neurologic disease and abortion in mare infected with lineage 1 West Nile virus, South Africa," *Emerging Infectious Diseases*, vol. 17, no. 8, pp. 1534–1536, 2011.
- [191] S. Larrieu, E. Cardinale, P. Ocquidant et al., "Case report: a fatal neuroinvasive West Nile virus infection in a traveler returning from Madagascar: clinical, epidemiological and veterinary investigations," *American Journal of Tropical Medicine and Hygiene*, vol. 89, no. 2, pp. 211–213, 2013.
- [192] E. S. Jentes, J. Robinson, B. W. Johnson et al., "Acute arboviral infections in Guinea, West Africa, 2006," *The American Journal of Tropical Medicine and Hygiene*, vol. 83, no. 2, pp. 388–394, 2010.
- [193] W. Wang, F. Sarkodie, K. Danso et al., "Seroprevalence of West Nile virus in Ghana," *Viral Immunology*, vol. 22, no. 1, pp. 17–22, 2009.
- [194] J. M. M. Lawson, D. Mounguengui, M. Ondounda, B. N. Edzang, J. Vandji, and R. Tchoua, "A case of meningo-encephalitis due to West Nile virus in Libreville, Gabon," *Medecine Tropicale*, vol. 69, no. 5, pp. 501–502, 2009.
- [195] M. Baba, C. H. Logue, B. Oderinde et al., "Evidence of arbovirus co-infection in suspected febrile malaria and typhoid patients in Nigeria," *Journal of Infection in Developing Countries*, vol. 7, no. 1, pp. 51–59, 2013.
- [196] A. G. Fall, A. Diaïté, M. T. Seck et al., "West Nile virus transmission in sentinel chickens and potential mosquito vectors, Senegal River Delta, 2008–2009," *International Journal of Environmental Research and Public Health*, vol. 10, no. 10, pp. 4718–4727, 2013.
- [197] M. K. Faulde, M. Spiesberger, and B. Abbas, "Sentinel site-enhanced near-real time surveillance documenting West Nile virus circulation in two Culex mosquito species indicating

- different transmission characteristics, Djibouti City, Djibouti," *Journal of the Egyptian Society of Parasitology*, vol. 42, no. 2, pp. 461–474, 2012.
- [198] C. Ochieng, J. Lutomiah, A. Makio et al., "Mosquito-borne arbovirus surveillance at selected sites in diverse ecological zones of Kenya; 2007–2012," *Virology Journal*, vol. 10, article 140, 2013.
- [199] K. C. Smithburn, J. A. Kerr, and P. B. Gatne, "Neutralizing antibodies against certain viruses in the sera of residents of India," *The Journal of Immunology*, vol. 72, no. 4, pp. 248–257, 1954.
- [200] T. R. Rao, "Immunological surveys of arbovirus infections in South-East Asia, with special reference to dengue, chikungunya, and Kyasanur Forest disease," *Bulletin of the World Health Organization*, vol. 44, no. 5, pp. 585–591, 1971.
- [201] J. Shukla, D. Saxena, S. Rathinam et al., "Molecular detection and characterization of West Nile virus associated with multifocal retinitis in patients from southern India," *International Journal of Infectious Diseases*, vol. 16, no. 1, pp. e53–e59, 2012.
- [202] A. Balakrishnan, D. K. Butte, and S. M. Jadhav, "Complete genome sequence of west nile virus isolated from Alappuzha district, Kerala, India," *Genome Announcements*, vol. 1, no. 3, 2013.
- [203] S. George, S. R. Prasad, J. A. Rao, P. N. Yergolkar, and C. V. Setty, "Isolation of Japanese encephalitis & West Nile viruses from fatal cases of encephalitis in Kolar district of Karnataka," *The Indian Journal of Medical Research*, vol. 86, pp. 131–134, 1987.
- [204] S. A. Khan, P. Dutta, A. M. Khan et al., "West nile virus infection, Assam, India," *Emerging Infectious Diseases*, vol. 17, no. 5, pp. 947–948, 2011.
- [205] S. A. Khan, P. Dutta, P. Chowdhury, J. Borah, R. Topno, and J. Mahanta, "Co-infection of arboviruses presenting as acute Encephalitis Syndrome," *Journal of Clinical Virology*, vol. 51, no. 1, pp. 5–7, 2011.
- [206] M. A. Darwish, H. Hoogstraal, T. J. Roberts, I. P. Ahmed, and F. Omar, "A sero-epidemiological survey for certain arboviruses (Togaviridae) in Pakistan," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 77, no. 4, pp. 442–445, 1983.
- [207] C. G. Hayes, S. Baqar, T. Ahmed, M. A. Chowdhry, and W. K. Reisen, "West Nile virus in Pakistan. 1. Sero-epidemiological studies in Punjab Province," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 76, no. 4, pp. 431–436, 1982.
- [208] A. Igarashi, M. Tanaka, K. Morita et al., "Detection of West Nile and Japanese encephalitis viral genome sequences in cerebrospinal fluid from acute encephalitis cases in Karachi, Pakistan," *Microbiology and Immunology*, vol. 38, no. 10, pp. 827–830, 1994.
- [209] M. Sugamata, A. Ahmed, T. Miura et al., "Seroepidemiological study of infection with West Nile virus in Karachi, Pakistan, in 1983 and 1985," *Journal of Medical Virology*, vol. 26, no. 3, pp. 243–247, 1988.
- [210] Centers for Disease Control and Prevention, *International Catalog of Arboviruses Including Certain Other Viruses of Vertebrates*, Centers for Disease Control and Prevention, Atlanta, Ga, USA, 2014.
- [211] C. Y. Ching, J. Casals, E. T. Bowen et al., "Arbovirus infections in Sarawak: the isolation of Kunjin virus from mosquitoes of the *Culex pseudovishnui* group," *Annals of Tropical Medicine and Parasitology*, vol. 64, no. 3, pp. 263–268, 1970.
- [212] N. Karabatsos, American Society of Tropical Medicine and Hygiene, American Committee on Arthropod-borne Viruses, and Rockefeller Foundation, *International Catalogue of Arboviruses, Including Certain Other Viruses of Vertebrates*, American Society of Tropical Medicine and Hygiene for The Subcommittee on Information Exchange of the American Committee on Arthropod-borne Viruses, 1985.
- [213] W. Rutvisuttinunt, S. K. Shrestha, P. Chinnawirotpisan et al., "Evidence of West Nile virus infection in Nepal," in *Proceedings of the 62nd American Society of Tropical Medicine and Hygiene Annual Meeting*, Washington, DC, USA, November 2013.
- [214] X. L. Li, S. H. Fu, W. B. Liu et al., "West nile virus infection in Xinjiang, China," *Vector-Borne and Zoonotic Diseases*, vol. 13, no. 2, pp. 131–133, 2013.
- [215] Q. R. Yang, "A study on arboviruse antibodies of birds in the Niao-Diao-Mountain area Eryan-county of Yunnan province," *Zhong Hua Liu Xing Bing Xue Za Zhi*, vol. 9, no. 3, pp. 150–153, 1988.
- [216] D. L. Lan, C. S. Wang, B. Deng et al., "Serological investigations on West Nile virus in birds and horses in Shanghai, China," *Epidemiology and Infection*, vol. 141, no. 3, pp. 596–600, 2013.
- [217] D. Lan, W. Ji, D. Yu et al., "Serological evidence of West Nile virus in dogs and cats in China," *Archives of Virology*, vol. 156, no. 5, pp. 893–895, 2011.
- [218] J. Y. Yeh, J. Y. Park, and E. N. Ostlund, "Serologic evidence of West Nile Virus in wild ducks captured in major inland resting sites for migratory waterfowl in South Korea," *Veterinary Microbiology*, vol. 154, no. 1-2, pp. 96–103, 2011.
- [219] R. L. Doherty, J. G. Carley, M. J. Mackerras, and E. N. Marks, "Studies of arthropod-borne virus infections in Queensland. III. Isolation and characterization of virus strains from wild-caught mosquitoes in North Queensland," *The Australian Journal of Experimental Biology and Medical Science*, vol. 41, pp. 17–39, 1963.
- [220] F. X. Heinz, M. S. Collett, R. H. Purcel et al., "Family: flaviviridae," in *Virus Taxonomy: Classification and Nomenclature of Viruses*, M. H. V. van Regenmortel, M. F. Fauquet, D. H. L. Bishop, R. J. M. Moormann, and et al, Eds., pp. 859–878, Academic Press, San Diego, Calif, USA, 1st edition, 2000.
- [221] R. C. Russell and D. E. Dwyer, "Arboviruses associated with human disease in Australia," *Microbes and Infection*, vol. 2, no. 14, pp. 1693–1704, 2000.
- [222] M. J. Frost, J. Zhang, J. H. Edmonds et al., "Characterization of virulent West Nile virus Kunjin strain, Australia, 2011," *Emerging Infectious Diseases*, vol. 18, no. 5, pp. 792–800, 2012.
- [223] R. A. Mann, M. Fegan, K. O'Riley, J. Motha, and S. Warner, "Molecular characterization and phylogenetic analysis of Murray Valley encephalitis virus and West Nile virus (Kunjin subtype) from an arbovirus disease outbreak in horses in Victoria, Australia, in 2011," *Journal of Veterinary Diagnostic Investigation*, vol. 25, no. 1, pp. 35–44, 2013.
- [224] N. A. Prow, "The changing epidemiology of Kunjin virus in Australia," *International Journal of Environmental Research and Public Health*, vol. 10, no. 12, pp. 6255–6272, 2013.
- [225] S. A. Williams, J. S. Richards, H. M. Faddy et al., "Low seroprevalence of murray valley encephalitis and kunjin viruses in an opportunistic serosurvey, Victoria 2011," *Australian and New Zealand Journal of Public Health*, vol. 37, no. 5, pp. 427–433, 2013.
- [226] V. Bardos, J. Adamcova, S. Dedei, N. Gjini, B. Rosicky, and A. Simkova, "Neutralizing antibodies against some neurotropic viruses determined in human sera in Albania," *Journal of Hygiene, Epidemiology, Microbiology, and Immunology*, vol. 3, pp. 277–282, 1959.

- [227] Z. Hubálek and J. Halouzka, "West Nile fever—a reemerging mosquito-borne viral disease in Europe," *Emerging Infectious Diseases*, vol. 5, no. 5, pp. 643–650, 1999.
- [228] A. R. Filipe, "Isolation in Portugal of West Nile virus from *Anopheles maculipennis* mosquitoes," *Acta Virologica*, vol. 16, no. 4, article 361, 1972.
- [229] E. Ernek, O. Kozuch, J. Nosek, J. Teplan, and C. Folk, "Arboviruses in birds captured in Slovakia," *Journal of Hygiene Epidemiology Microbiology and Immunology*, vol. 21, no. 3, pp. 353–359, 1977.
- [230] Z. Hubalek, J. Halouzka, Z. Juricova, and O. Sebesta, "First isolation of mosquito-borne west nile virus in the Czech Republic," *Acta Virologica*, vol. 42, no. 2, pp. 119–120, 1998.
- [231] E. Molnár, M. S. Gulyás, L. Kubinyi et al., "Studies on the occurrence of tick-borne encephalitis in Hungary," *Acta veterinaria Academiae Scientiarum Hungaricae*, vol. 26, no. 4, pp. 419–437, 1976.
- [232] H. G. Zeller and I. Schuffenecker, "West Nile virus: an overview of its spread in Europe and the Mediterranean basin in contrast to its spread in the Americas," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 23, no. 3, pp. 147–156, 2004.
- [233] P. Couissinier-Paris, "West Nile virus in Europe and Africa: still minor pathogen, or potential threat to public health?" *Bulletin de la Societe de Pathologie Exotique*, vol. 99, no. 5, pp. 348–354, 2006.
- [234] T. Bakonyi, E. Ferenczi, K. Erdélyi et al., "Explosive spread of a neuroinvasive lineage 2 West Nile virus in Central Europe, 2008/2009," *Veterinary Microbiology*, vol. 165, no. 1-2, pp. 61–70, 2013.
- [235] P. Calistri, A. Giovannini, Z. Hubalek et al., "Epidemiology of West Nile in Europe and in the Mediterranean basin," *The Open Virology Journal*, vol. 4, pp. 29–37, 2010.
- [236] B. Murgue, S. Murri, S. Zientara, B. Durand, J.-P. Durand, and H. Zeller, "West Nile outbreak in horses in Southern France, 2000: the return after 35 years," *Emerging Infectious Diseases*, vol. 7, no. 4, pp. 692–696, 2001.
- [237] A. Mailles, P. Dellamonica, H. Zeller et al., "Human and equine West Nile virus infections in France, August-September 2003," *Eurosurveillance*, vol. 7, no. 43, article 1, 2003, <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2312>.
- [238] B. Durand, G. Dauphin, H. Zeller et al., "Serosurvey for West Nile virus in horses in southern France," *Veterinary Record*, vol. 157, no. 22, pp. 711–713, 2005.
- [239] G. L. Autorino, A. Battisti, V. Deubel et al., "West Nile virus epidemic in horses, Tuscany region, Italy," *Emerging Infectious Diseases*, vol. 8, no. 12, pp. 1372–1378, 2002.
- [240] G. Rezza, "Chikungunya and West Nile virus outbreaks: what is happening in north-eastern Italy," *European Journal of Public Health*, vol. 19, no. 3, pp. 236–237, 2009.
- [241] C. Rizzo, P. Salcuni, L. Nicoletti et al., "Epidemiological surveillance of West Nile neuroinvasive diseases in Italy, 2008 to 2011," *Eurosurveillance*, vol. 17, no. 20, 2012.
- [242] A. E. Platonov, V. A. Tolpin, K. A. Gridneva et al., "The incidence of west nile disease in russia in relation to climatic and environmental factors," *International Journal of Environmental Research and Public Health*, vol. 11, no. 2, pp. 1211–1232, 2014.
- [243] O. Engler, G. Savini, A. Papa et al., "European surveillance for West Nile virus in mosquito populations," *International Journal of Environmental Research and Public Health*, vol. 10, no. 10, pp. 4869–4895, 2013.
- [244] L. Barzon, M. Pacenti, E. Franchin et al., "Large human outbreak of West Nile virus infection in north-eastern Italy in 2012," *Viruses*, vol. 5, no. 11, pp. 2825–2839, 2013.
- [245] L. Barzon, M. Pacenti, E. Franchin et al., "The complex epidemiological scenario of West Nile virus in Italy," *International Journal of Environmental Research and Public Health*, vol. 10, no. 10, pp. 4669–4689, 2013.
- [246] L. Barzon, M. Pacenti, E. Franchin et al., "Whole genome sequencing and phylogenetic analysis of West Nile virus lineage 1 and lineage 2 from human cases of infection, Italy, August 2013," *Eurosurveillance*, vol. 18, no. 38, Article ID 20597, 2013.
- [247] C. Napoli, A. Bella, S. Declich et al., "Integrated human surveillance systems of West Nile virus infections in Italy: the 2012 experience," *International Journal of Environmental Research and Public Health*, vol. 10, no. 12, pp. 7180–7192, 2013.
- [248] A. Papa, E. Papadopolou, E. Gavana, S. Kalaitzopoulou, and S. Mourelatos, "Detection of west nile virus lineage 2 in culex mosquitoes, Greece, 2012," *Vector-Borne and Zoonotic Diseases*, vol. 13, no. 9, pp. 682–684, 2013.
- [249] I. Jesús-de La Calle, M. J. Espinosa-García, S. Pérez-Ramos, and E. Cruz-Rosales, "First confirmed cases of human meningoencephalitis due to West Nile virus in Andalusia, Spain," *Enfermedades Infecciosas y Microbiología Clínica*, vol. 30, no. 7, pp. 426–427, 2012.
- [250] K. Stiasny, S. W. Aberle, and F. X. Heinzl, "Retrospective identification of human cases of west nile virus infection in Austria (2009 to 2010) by serological differentiation from Usutu and other flavivirus infections," *Eurosurveillance*, vol. 18, no. 43, 2013.
- [251] E. Merdić, L. Perić, N. Pandak et al., "West Nile virus outbreak in humans in Croatia, 2012," *Collegium Antropologicum*, vol. 37, no. 3, pp. 943–947, 2013.
- [252] N. Popovic, B. Milosevic, A. Urosevic et al., "Outbreak of West Nile virus infection among humans in Serbia," *Eurosurveillance*, vol. 18, no. 43, 2013.
- [253] I. Pem-Novosel, T. Vilibic-Cavlek, I. Gjenero-Margan et al., "First outbreak of west nile virus neuroinvasive disease in humans, Croatia, 2012," *Vector-Borne and Zoonotic Diseases*, vol. 14, no. 1, pp. 82–84, 2014.
- [254] A. Esteves, A. P. G. Almeida, R. P. Galão et al., "West Nile virus in Southern Portugal, 2004," *Vector-Borne and Zoonotic Diseases*, vol. 5, no. 4, pp. 410–413, 2005.
- [255] V. Sambri, M. Capobianchi, R. Charrel et al., "West Nile virus in Europe: emergence, epidemiology, diagnosis, treatment, and prevention," *Clinical Microbiology and Infection*, vol. 19, no. 8, pp. 699–704, 2013.
- [256] I. C. Kurolt, V. Krajinovic, A. Topic, I. Kuzman, B. Barsic, and A. Markotic, "First molecular analysis of West Nile virus during the 2013 outbreak in Croatia," *Virus Research*, vol. 189, pp. 63–66, 2014.
- [257] T. Petrović, A. B. Blázquez, D. Lupulović et al., "Monitoring West Nile virus (WNV) infection in wild birds in Serbia during 2012: first isolation and characterisation of WNV strains from Serbia," *Eurosurveillance*, vol. 18, no. 44, 2013.
- [258] G. Savini, G. Capelli, F. Monaco et al., "Evidence of West Nile virus lineage 2 circulation in Northern Italy," *Veterinary Microbiology*, vol. 158, no. 3-4, pp. 267–273, 2012.
- [259] G. Valiakos, A. Touloudi, C. Iacovakis et al., "Molecular detection and phylogenetic analysis of West Nile virus lineage 2 in sedentary wild birds (Eurasian magpie), Greece, 2010," *Eurosurveillance*, vol. 16, no. 18, 2011.

- [260] E. Wodak, S. Richter, Z. Bagó et al., "Detection and molecular analysis of West Nile virus infections in birds of prey in the Eastern part of Austria in 2008 and 2009," *Veterinary Microbiology*, vol. 149, no. 3-4, pp. 358-366, 2011.
- [261] A. C. Brault, C. Y.-H. Huang, S. A. Langevin et al., "A single positively selected West Nile viral mutation confers increased virogenesis in American crows," *Nature Genetics*, vol. 39, no. 9, pp. 1162-1166, 2007.
- [262] A. Papa, T. Bakonyi, K. Xanthopoulou, A. Vázquez, A. Tenorio, and N. Nowotny, "Genetic characterization of west nile virus lineage 2, Greece, 2010," *Emerging Infectious Diseases*, vol. 17, no. 5, pp. 920-922, 2011.
- [263] D. Morgan, "Control of arbovirus infections by a coordinated response: West Nile Virus in England and Wales," *FEMS Immunology and Medical Microbiology*, vol. 48, no. 3, pp. 305-312, 2006.
- [264] S. Linke, M. Niedrig, A. Kaiser et al., "Serologic evidence of West Nile virus infections in wild birds captured in Germany," *The American Journal of Tropical Medicine and Hygiene*, vol. 77, no. 2, pp. 358-364, 2007.
- [265] C. Laubli, S. Neves da Costa Monteiro Pires, C. Griot, and E. Breidenbach, "West nile virus epizootic situation in Switzerland," 2006, <http://www.bvet.admin.ch/gesundheit.tiere/00315/00317/02600/index.html>.
- [266] V. A. Brugman, D. L. Horton, L. P. Phipps et al., "Epidemiological perspectives on West Nile virus surveillance in wild birds in Great Britain," *Epidemiology and Infection*, vol. 141, no. 6, pp. 1134-1142, 2013.
- [267] A. Buckley, A. Dawson, S. R. Moss, S. A. Hinsley, P. E. Bellamy, and E. A. Gould, "Serological evidence of West Nile virus, Usutu virus and Sindbis virus infection of birds in the UK," *Journal of General Virology*, vol. 84, no. 10, pp. 2807-2817, 2003.
- [268] A. Buckley, A. Dawson, and E. A. Gould, "Detection of seroconversion to West Nile virus, Usutu virus and Sindbis virus in UK sentinel chickens," *Virology Journal*, vol. 3, article 71, 2006.
- [269] L. P. Phipps, J. P. Duff, J. P. Holmes et al., "Surveillance for West Nile virus in British birds (2001 to 2006)," *The Veterinary Record*, vol. 162, no. 13, pp. 413-415, 2008.
- [270] Z. Hubálek, E. Wegner, J. Halouzka et al., "Serologic survey of potential vertebrate hosts for West Nile virus in Poland," *Viral Immunology*, vol. 21, no. 2, pp. 247-253, 2008.
- [271] R. N. Charrel, A. C. Brault, P. Gallian et al., "Evolutionary relationship between Old World West Nile virus strains: evidence for viral gene flow between Africa, the Middle East, and Europe," *Virology*, vol. 315, no. 2, pp. 381-388, 2003.
- [272] "Human West Nile virus surveillance—Connecticut, New Jersey, and New York, 2000," *Morbidity and Mortality Weekly Report*, vol. 50, no. 14, pp. 265-268, 2001.
- [273] C. T. Davis, G. D. Ebel, R. S. Lanciotti et al., "Phylogenetic analysis of North American West Nile virus isolates, 2001-2004: evidence for the emergence of a dominant genotype," *Virology*, vol. 342, no. 2, pp. 252-265, 2005.
- [274] G. D. Ebel, J. Carricaburu, D. Young, K. A. Bernard, and L. D. Kramer, "Genetic and phenotypic variation of West Nile virus in New York, 2000-2003," *The American Journal of Tropical Medicine and Hygiene*, vol. 71, no. 4, pp. 493-500, 2004.
- [275] R. M. Moudy, M. A. Meola, L.-L. L. Morin, G. D. Ebel, and L. D. Kramer, "A newly emergent genotype of West Nile virus is transmitted earlier and more efficiently by Culex mosquitoes," *The American Journal of Tropical Medicine and Hygiene*, vol. 77, no. 2, pp. 365-370, 2007.
- [276] K. W. Snapinn, E. C. Holmes, D. S. Young, K. A. Bernard, L. D. Kramer, and G. D. Ebel, "Declining growth rate of West Nile virus in North America," *Journal of Virology*, vol. 81, no. 5, pp. 2531-2534, 2007.
- [277] O. Komar, M. B. Robbins, G. G. Contreras et al., "West Nile virus survey of birds and mosquitoes in the Dominican Republic," *Vector-Borne and Zoonotic Diseases*, vol. 5, no. 2, pp. 120-126, 2005.
- [278] Centers for Disease Control and Prevention, "West Nile virus statistics and maps," 2013, <http://www.cdc.gov/westnile/stats-Maps/>.
- [279] L. R. Petersen, P. J. Carson, B. J. Biggerstaff, B. Custer, S. M. Borchardt, and M. P. Busch, "Estimated cumulative incidence of West Nile virus infection in US adults, 1999-2010," *Epidemiology & Infection*, vol. 141, no. 3, pp. 591-595, 2013.
- [280] P. Sockett, "The incursion and expansion of West Nile Virus into Canada," 2005, <http://www.webbertraining.com/files/library/docs/26.pdf>.
- [281] Public Health Agency of Canada, "Summary of Human Surveillance Table: (2008-2012)(2002-2007)," 2013, <http://www.phac-aspc.gc.ca/wnv-vwn/mon-hmnsurv-archive-eng.php#a-2008.12>.
- [282] D. Roth, B. Henry, S. Mak et al., "West Nile Virus range expansion into British Columbia," *Emerging Infectious Diseases*, vol. 16, no. 8, pp. 1251-1258, 2010.
- [283] Public Health Agency of Canada, "Human Surveillance," 2013, <http://www.phac-aspc.gc.ca/wnv-vwn/mon-hmnsurv-eng.php>.
- [284] Caribbean Epidemiology Centre, *West Nile Virus in Cayman Islands*, Caribbean Epidemiology Centre, Trinidad and Tobago, Spain, 2001.
- [285] A. P. Dupuis II, P. P. Marra, and L. D. Kramer, "Serologic evidence of West Nile virus transmission, Jamaica, West Indies," *Emerging Infectious Diseases*, vol. 9, no. 7, pp. 860-863, 2003.
- [286] O. Komar, M. B. Robbins, K. Klenk et al., "West Nile virus transmission in resident birds, Dominican Republic," *Emerging Infectious Diseases*, vol. 9, no. 10, pp. 1299-1302, 2003.
- [287] R. Quirin, M. Salas, S. Zientara et al., "West Nile Virus, Guadeloupe," *Emerging Infectious Diseases*, vol. 10, no. 4, pp. 706-708, 2004.
- [288] Caribbean Epidemiology Centre, "Recommendations for West Nile Surveillance in the Caribbean," 2004, <http://www.carec.org/west-nile-2004/>.
- [289] N. Komar and G. G. Clark, "West Nile virus activity in Latin America and the Caribbean," *Revista Panamericana de Salud Publica*, vol. 19, no. 2, pp. 112-117, 2006.
- [290] M. Pupo, M. G. Guzmán, R. Fernández et al., "West Nile virus infection in humans and horses, Cuba," *Emerging Infectious Diseases*, vol. 12, no. 6, pp. 1022-1024, 2006.
- [291] A. P. Dupuis II, P. P. Marra, R. Reitsma, M. J. Jones, K. L. Louie, and L. D. Kramer, "Short report: serologic evidence for West Nile virus transmission in Puerto Rico and Cuba," *The American Journal of Tropical Medicine and Hygiene*, vol. 73, no. 2, pp. 474-476, 2005.
- [292] E. A. Hunsperger, K. L. McElroy, K. Bessoff, C. Colón, R. Barrera, and J. L. Muñoz-Jordán, "West Nile virus from blood donors, vertebrates, and mosquitoes, Puerto Rico, 2007," *Emerging Infectious Diseases*, vol. 15, no. 8, pp. 1298-1300, 2009.
- [293] R. Barrera, E. Hunsperger, J. L. Muñoz-Jordán et al., "Short report: first isolation of West Nile virus in the Caribbean," *The American Journal of Tropical Medicine and Hygiene*, vol. 78, no. 4, pp. 666-668, 2008.

- [294] M. E. Beatty, E. Hunsperger, E. Long et al., "Mosquitoborne infections after Hurricane Jeanne, Haiti, 2004," *Emerging Infectious Diseases*, vol. 13, no. 2, pp. 308–310, 2007.
- [295] J. G. Estrada-Franco, R. Navarro-Lopez, D. W. C. Beasley et al., "West Nile virus in Mexico: evidence of widespread circulation since July 2002," *Emerging Infectious Diseases*, vol. 9, no. 12, pp. 1604–1607, 2003.
- [296] D. Elizondo-Quiroga, C. T. Davis, I. Fernandez-Salas et al., "West Nile virus isolation in human and mosquitoes, Mexico," *Emerging Infectious Diseases*, vol. 11, no. 9, pp. 1449–1452, 2005.
- [297] C. Rios-Ibarra, B. J. Blitvich, J. Farfan-Ale et al., "Fatal human case of West Nile virus disease, Mexico, 2009," *Emerging Infectious Diseases*, vol. 16, no. 4, pp. 741–743, 2010.
- [298] S. Guerrero-Sánchez, S. Cuevas-Romero, N. M. Nemeth et al., "West Nile virus infection of birds, Mexico," *Emerging Infectious Diseases*, vol. 17, no. 12, pp. 2245–2252, 2011.
- [299] D. W. C. Beasley, C. T. Davis, J. Estrada-Franco et al., "Genome sequence and attenuating mutations in Nile virus isolate from Mexico," *Emerging Infectious Diseases*, vol. 10, no. 12, pp. 2221–2224, 2004.
- [300] A. C. Brault, S. A. Langevin, W. N. Ramey et al., "Reduced avian virulence and viremia of West Nile virus isolates from Mexico and Texas," *The American Journal of Tropical Medicine and Hygiene*, vol. 85, no. 4, pp. 758–767, 2011.
- [301] L. Cruz, V. M. Cardenas, M. Abarca et al., "Short report: serological evidence of West Nile virus activity in El Salvador," *The American Journal of Tropical Medicine and Hygiene*, vol. 72, no. 5, pp. 612–615, 2005.
- [302] M. E. Morales-Betoulle, N. Komar, N. A. Panella et al., "West Nile virus ecology in a tropical ecosystem in Guatemala," *The American Journal of Tropical Medicine and Hygiene*, vol. 88, no. 1, pp. 116–126, 2013.
- [303] J. Hobson-Peters, C. Arévalo, W. Y. Cheah et al., "Detection of antibodies to West Nile virus in horses, Costa Rica, 2004," *Vector-Borne and Zoonotic Diseases*, vol. 11, no. 8, pp. 1081–1084, 2011.
- [304] L. Berrocal, J. Peña, M. González, and S. Mattar, "West Nile virus; ecology and epidemiology of an emerging pathogen in Colombia," *Revista de Salud Publica*, vol. 8, no. 2, pp. 218–228, 2006.
- [305] S. Mattar, N. Komar, G. Young, J. Alvarez, and M. Gonzalez, "Seroconversion for West Nile and St. Louis encephalitis viruses among sentinel horses in Colombia," *Memorias do Instituto Oswaldo Cruz*, vol. 106, no. 8, pp. 976–979, 2011.
- [306] M. A. Morales, M. Barrandeguy, C. Fabbri et al., "West Nile virus isolation from equines in Argentina, 2006," *Emerging Infectious Diseases*, vol. 12, no. 10, pp. 1559–1561, 2006.
- [307] L. A. Diaz, N. Komar, A. Visintin et al., "West Nile virus in birds, Argentina," *Emerging Infectious Diseases*, vol. 14, no. 4, pp. 689–691, 2008.
- [308] I. Bosch, F. Herrera, J.-C. Navarro et al., "West Nile virus, Venezuela," *Emerging Infectious Diseases*, vol. 13, no. 4, pp. 651–653, 2007.
- [309] A. Pauvolid-Corrêa, M. A. Morales, S. Levis et al., "Neutralising antibodies for West Nile virus in horses from Brazilian Pantanal," *Memorias do Instituto Oswaldo Cruz*, vol. 106, no. 4, pp. 467–474, 2011.
- [310] T. Ometto, E. L. Durigon, J. de Araujo et al., "West Nile virus surveillance, Brazil, 2008–2010," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 107, no. 11, Article ID trt081, pp. 723–730, 2013.
- [311] V. Melandri, A. É. Guimarães, N. Komar et al., "Serological detection of West Nile virus in horses and chicken from Pantanal, Brazil," *Memorias do Instituto Oswaldo Cruz*, vol. 107, no. 8, pp. 1073–1075, 2012.
- [312] A. Pauvolid-Correa, Z. Campos, R. Juliano, J. Velez, R. M. Nogueira, and N. Komar, "Serological evidence of widespread circulation of West Nile virus and other flaviviruses in equines of the Pantanal, Brazil," *PLoS Neglected Tropical Diseases*, vol. 8, Article ID e2706, 2014.
- [313] J. R. Silva, L. C. Medeiros, V. P. Reis et al., "Serologic survey of West Nile virus in horses from Central-West, Northeast and Southeast Brazil," *Memorias do Instituto Oswaldo Cruz*, vol. 108, no. 7, pp. 921–923, 2013.
- [314] C. N. Soares, M. J. C. Castro, J. M. Peralta, M. R. G. de Freitas, and M. Puccioni-Sohler, "Is West Nile virus a potential cause of central nervous system infection in Brazil?" *Arquivos de Neuro-Psiquiatria*, vol. 68, no. 5, pp. 761–763, 2010.
- [315] B. M. Forshey, C. Guevara, V. A. Laguna-Torres et al., "Arboviral etiologies of acute febrile illnesses in western south America, 2000–2007," *PLoS Neglected Tropical Diseases*, vol. 4, no. 8, article e787, 2010.
- [316] M. Mazzei, G. Savini, D. G. Annapia et al., "West Nile seroprevalence study in Bolivian horses, 2011," *Vector-Borne and Zoonotic Diseases*, vol. 13, no. 12, pp. 894–896, 2013.
- [317] J. E. Osorio, K. A. Ciudoderis, J. G. Lopera et al., "Characterization of West Nile viruses isolated from captive American flamingoes (*Phoenicopterus ruber*) in Medellín, Colombia," *The American Journal of Tropical Medicine and Hygiene*, vol. 87, no. 3, pp. 565–572, 2012.

