TROPICAL, TRAVEL AND EMERGING INFECTIONS (LH CHEN AND F NORMAN, SECTION EDITORS)

West Nile virus: another emerging arboviral risk for travelers?

Chinmay Jani[1,2] · Loukas Kakoullis[1,2] · Nour Abdallah[4] · Christian Mouchati[3,5] · Stephanie Page[1,2] · Robert Colgrove[1,2,6] · Lin H. Chen[1,2,6,7]

Abstract

Purpose of Review West Nile virus (WNV) is an arbovirus transmitted by mosquitos of the genus *Culex*. Manifestations of WNV infection range from asymptomatic to devastating neuroinvasive disease leading to flaccid paralysis and death. This review examines WNV epidemiology and ecology, with an emphasis on travel-associated infection.

Recent Findings WNV is widespread, including North America and Europe, where its range has expanded in the past decade. Rising temperatures in temperate regions are predicted to lead to an increased abundance of *Culex* mosquitoes and an increase in their ability to transmit WNV. Although the epidemiologic patterns of WNV appear variable, its geographic distribution most certainly will continue to increase. Travelers are at risk for WNV infection and its complications. Literature review identified 39 cases of documented travel-related WNV disease, the majority of which resulted in adverse outcomes, such as neuroinvasive disease, prolonged recovery period, or death.

Summary The prediction of WNV risk is challenging due to the complex interactions of vector, pathogen, host, and environment. Travelers planning to visit endemic areas should be advised regarding WNV risk and mosquito bite prevention. Evaluation of ill travelers with compatible symptoms should consider the diagnosis of WNV for those visiting in endemic areas as well as for those returning from destinations with known WNV circulation.

Keywords Flavivirus · Neuroinvasive · One Health · *Culex* mosquito · Emerging infection · Epidemiology · Imported

Introduction

West Nile virus (WNV), deriving its name from the West Nile district of Uganda [1], is a mosquito-borne arbovirus belonging to the Flaviviridae family. Now commonly found

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✉ Chinmay Jani
Chinmay.jani@mah.harvard.edu; ctjani1494@gmail.com

Loukas Kakoullis
Loukas.kakoullis@mah.harvard.edu

Nour Abdallah
nour.abdallah29@gmail.com

Christian Mouchati
cmouchati@gmail.com

Stephanie Page
spage1@mah.harvard.edu

Robert Colgrove
robert_colgrove@hms.harvard.edu

Lin H. Chen
lchen@hms.harvard.edu

1   Department of Medicine, Mount Auburn Hospital, 330 Mount Auburn St Cambridge, Cambridge, MA, USA

2   Harvard Medical School, Boston, MA, USA

3   University Hospitals Cleveland Medical Center, Cleveland, OH, USA

4   Department of Urology Research, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

5   Department of Pediatrics, Case Western Reserve University, Cleveland, OH, USA

6   Division of Infectious Diseases, Mount Auburn Hospital, Cambridge, MA, USA

7   Travel Medicine Center, Mount Auburn Hospital, Cambridge, MA, USA

in Africa, Europe, the Middle East, North America, and West Asia, WNV epidemiology has been evolving in the past decades [2–4]. The virus itself has undergone adaptive genetic changes while expanding its geographic areas [5]. The epidemic of 1999 in the New York City area is a reminder of the ability of such viruses to leap from one hemisphere to another via migratory birds [6].

With birds and mosquitos as its natural hosts, the virus can infect a wide variety of other vertebrates as dead-end hosts, causing severe disease in some, notably humans and horses [4, 6]. In humans, the clinical course of WNV infection ranges from asymptomatic or mild febrile illness to severe neurological manifestations (West Nile neuroinvasive disease; WNND) and fatalities [2, 4, 6]. The elderly and immunocompromised hosts are at increased risk for disseminated WNV infection and for developing fatal encephalitis [7]. In animal models, an overactive inflammatory response can lead to increased blood–brain barrier (BBB) permeability for the viruses, leading to neuronal death [7]. Despite the significance of neurological involvement in severe disease, the exact mechanism is not clear. To date, the primary treatment of WNV infection has remained supportive with potential benefits from corticosteroids and IVIG [8, 9]. Multiple outbreaks have occurred in the past two decades in different parts of the world, including in travelers [10, 11]. With the ongoing SARS-CoV-2 pandemic complicating the differential diagnosis of febrile illnesses, it is timely to review WNV outbreaks and understand its evolving epidemiology. The objective of this article is to review the epidemiology, transmission, and clinical course of WNV with an emphasis on travel-related infections. We conducted a PubMed search using the syntax (west nile) AND (travelers) or (imported) to obtain the cases identified in travelers.

Epidemiology

The first case of WNV was diagnosed in a woman presenting with a febrile illness in 1937 in Uganda [1]. After that, cases were reported in Israel, Egypt, France, and South Africa throughout the 1950s to 1970s, followed by large outbreaks in Romania and Russia in the 1990s [12–14]. WNV infections were reported for the first time in Algeria and Morocco in 1994 and 1996, respectively [15•]. In 1999, the first WNV cases in the Western Hemisphere were identified in New York City, where 59 patients were hospitalized, among whom 7 died (12%) [16]. Since this outbreak, it has spread throughout North America, with many reported cases in humans, while sporadic cases as well as several outbreaks have been reported in Europe. To explain the difference between the two regions, various hypotheses have been suggested, including the difference in virulence, susceptibility of the bird species, the competence of mosquitoes, and

partial protection due to cross-reactivity with other flaviviruses in Europe, such as the tick-borne encephalitis virus [17].

In the twenty-first century, major WNV outbreaks occurred in Argentina, Canada, China, and throughout Europe, notably in Hungary in 2008, Greece in 2010, Italy in 2011, and Serbia in 2012 [18–25]. In Europe, there were, on average, 18 newly affected areas annually between 2011 and 2017, and 45 additional areas reported in 2018, with most infections occurring from early summer to early autumn and peaking in August [26•]. Until 2017, the countries with the highest number of cases were Greece, Italy, Romania, and Hungary [27••]. In 2018, Hungary reported 215 locally acquired and 10 imported human infections [28]. In Turkey, where Europe and Asia converge, WNV exposure in humans has been documented in all main regions of Anatolia and Thrace over a relatively long period (1973–2019) [29], while cases have been exported to other countries, such as Hungary, through returning travelers [28]. The European CDC reported a 7.2-fold increase in cases from 2017 to 2018, especially in Bulgaria (15-fold), France (13.5-fold), and Italy (10.9-fold), which is partially attributed to the unusually hot summers. In 2020, a major outbreak was reported in Spain with 77 confirmed cases of WNV, of which 72 developed neuroinvasive disease and 7 died, partly attributed to reduced activities for vector control during that season, among other factors [30–33]. In 2021, 54 infections were reported through October 7, 2021 in Greece, 52 in Italy, 7 in Hungary, 7 in Romania, 6 in Spain, 3 in Austria, 3 in Germany, and 17 in Serbia, with cases reported for the first time in Spree-Neiße in Germany and La Spezia in Italy [34].

In the USA, WNV was the most common cause of neuroinvasive arboviral disease in 2018; however, neuroinvasive disease occurred at an incidence of 0.51 per 100,000 in 2018, approximately 25% higher than the median incidence of 0.41 during 2008–2017 [35]. According to the CDC, between 2009 and 2018, the highest number of total cases in the USA occurred in California ($n = 2819$), Texas ($n = 2043$), Illinois ($n = 728$), and Arizona ($n = 632$), with North Dakota recording the highest average annual incidence of neuroinvasive disease (3.16 cases per 100,000 population), followed by South Dakota (3.06), Nebraska (1.95), and Mississippi (1.17) [35]. In 2019, WNV continued to be the most common cause of domestic arboviral neuroinvasive disease in the USA; however, an annual incidence of 0.19 per 100,000 was 53% lower than the median annual incidence during 2009–2018. The Midwestern and South Central states, particularly Texas, saw the widest decrease, as opposed to the Mountain region, where the number of cases exceeded the annual median incidence during 2009–2018 [36]. For 2021 through January 11, 2022, 2695 cases were reported in the USA, of which 1855 presented with WNND (69%), 840 presented with non-neuroinvasive disease, and 191 died (7%)

[37]. Most cases were reported in Arizona (1645), Colorado (174), and California (115) [37].

Sporadic cases have also been reported from Central and South America from equines, birds, and humans [38, 39]. In 2003, a human case of WNND was diagnosed in the Bahamas, followed by 6 human cases (3 with encephalitis) in Northern Mexico in 2004 [39, 40]. In 2005, WNND cases were announced in central Cuba.

In Asia, very few human cases have been reported. Even though WNV has been isolated from pigeons and migratory birds in Korea, the first reported human case was from a traveler on a business trip to Guinea, Africa [41]. In India, initial WNV antibodies were first detected in Mumbai in 1952. In contrast to western countries, there were frequent reports of children succumbing to WNV infection in the 1980s. Similarly, serological evidence of WNV infection was reported from Pakistan in the 1970s. However, neuroinvasive disease cases from India, Pakistan, and Sri Lanka were not reported until 2011–2015. In 2011, an outbreak was reported in the southern State of India, Kerala [42]. In China, outbreaks of viral encephalitis caused by WNV infection have been recorded locally since 2013 [43]. In Australia, Kunjin virus lineage (1b) is common in the Northern region. However, clinical cases are found to be rare [44].

The epidemiological situation in Africa is less clear. Challenges lie in the similarity of WNV symptoms with those of other arboviruses and tropical diseases such as malaria and typhoid fever, poor public health data sharing, and potential cross-reactivity resulting from the use of non-specific WNV neutralization assays, and inconsistent surveillance [15•].

The Virus

WNV is an enveloped, 11-kilobase, positive sense, single-stranded RNA virus in the family Flaviviridae, phylogenetically related to other mosquito-borne flaviviruses [45], and most closely related to the neurotropic flaviviruses, Japanese encephalitis virus, and St. Louis encephalitis virus. Like other flaviviruses, the virions are spherical particles, 45–50 nm in diameter, with icosahedral symmetry. The E protein lies flat over the lipid envelope, forming a nearly complete shell around it. The E protein binds to multiple receptors on the surface of diverse cell types, facilitates virion entry via receptor-mediated endocytosis, and is the primary target of neutralizing antibodies. Host ribosomes translate the (+) sense viral RNA into a single, long polypeptide, which is subsequently cleaved by viral and host proteases into the mature viral structural and non-structural proteins. The viral RNA-dependent RNA polymerase replicates viral genomes. Progeny genomes are packaged within nascent viral capsids, which assemble into virions on the endoplasmic reticulum, transit through the Golgi apparatus,

and are secreted via exocytic vesicles that bud through the plasma membrane after a furin-mediated cleavage of the viral prM protein[45].

Up to 9 lineages of WNV have been recognized (Table 1) with varying degrees of neuroinvasiveness; most symptomatic outbreaks are attributed to lineages 1 and 2 [46, 47]. Lineage 1 is subclassified into the more severe clade 1a, which originated from Egypt and currently circulating in Europe, Africa, and the Americas, and clade 1b (Kunjin virus) isolated in Oceania and rarely causes a neurological disease [48–52]. Lineage 2 originated from Uganda and was initially contained in Africa but emerged later in 2004 in Europe, especially in Hungary, Greece, and Italy [22, 23, 51–54]. The other lineages are less widespread; lineage 3 (Rabensburg virus) was isolated in the Czech Republic, lineage 4 in Russia, lineage 5 (also considered clade 1c of lineage 1) in India, lineage 6 originally from Malaysia and then in Spain, lineage 7 (Koutango virus) in Senegal without any reported natural human infection yet, lineage 8 in Senegal, and lineage 9 (sub-lineage of lineage 4) in Austria [51, 55–60]. Interestingly, a lower frequency of neuroinvasive disease was seen in the African outbreaks, compared to the American ones, despite the circulation of lineages 1, 2, 7, and 8 and the high antibody seroprevalence in sampled humans [46]. In the 2011 India outbreak, most cases were found to be infected with lineage I. However, lineage V (initially subclassified as 1c) is now prevalent in the Northeast region of India [61•].

Vector and Transmission

The primary vector of WNV are the mosquitos of the *Culex* genus. In the USA, WNV is transmitted mainly through *C. pipiens*, *C. tarsalis*, and *C. quinquefasciatus* [62], while in Europe, the predominant vector is *C. pipiens*; regardless, over 50 mosquito species have been found to carry the virus in North America alone[63]. Furthermore, although the presence of WNV has also been reported in *Aedes* spp., these

Table 1 West Nile virus lineages

Lineages	Geographic distribution
1a	Europe, Africa, and Americas
1b	Oceania
2	Africa and Europe (Hungary, Greece, and Italy)
3	Czech Republic
4	Russia
5	India (Also considered 1c)
6	Spain
7	Senegal (no reports of human infection)
8	Senegal
9	Austria (considered sub-lineage of 4)

mosquitoes are not regarded as significant vectors of the virus in the wild [64, 65]. *Culex* mosquitos are mostly night biters, with their feeding activity peaking between dusk and dawn [66]. The infection of migratory species of birds can also enable the virus to travel much further, and introduce WNV to new locations [67]. In addition to mosquito transmission, WNV transmission has also occurred through other routes, although rarely, such as organ transplantation, blood transfusions, and breast milk, or even vertically [4].

The primary vertebrate host of WNV is birds, with the virus maintained in an enzootic cycle between birds and *Culex* spp. mosquitos. In the USA, the American robin is considered the primary host for WNV, as vectors display a feeding preference for their species [64, 68]. The transmission cycle begins when a female mosquito takes a blood meal from a viremic host. The ingested viral particles end up in the midgut of the insect. After infecting and replicating within the midgut epithelium, they are released into the mosquito hemolymph, the cavity containing the insect's circulatory fluid. From there, the virus disseminates throughout the insect's body, reaching the salivary glands, where it accumulates and can be transmitted to a new host during the next blood meal [69]. Mammals are considered "dead-end" hosts for the virus, as the levels of viremia achieved in mammals are not adequate for transmission to other mosquitos, terminating the cycle of WNV transmission[2].

After the ingestion of the blood meal, the female *Culex* spp. mosquito searches for a water source, where it will lay between 100 and 300 eggs. The eggs hatch into larvae that mature into pupae, from which the adult mosquito finally emerges [70]. This process is highly temperature-dependent, and the duration of each stage varies significantly depending on temperature. Eggs cannot hatch in temperatures under 7 °C, require 10 days of incubation at 10 °C or 3 days at 20 °C, while they can hatch after a single day at 30 °C. Similarly, larvae can evolve into adult mosquitos in a week or less at 30 °C. Still, at 15 °C, they may require 3 weeks or more in order to reach adulthood [71].

Additionally, temperature plays a significant role in the external incubation period (EIP) of WNV, defined as the time between ingesting an infectious blood meal until the moment the mosquito can transmit the virus to a new host. EIP is measured in degree-days, the product of the average daily temperature multiplied by days with a temperature over the minimum developmental threshold, i.e., the minimum temperature at which the virus develops. The EIP for WNV in *Culex* mosquitos has been estimated to be 109 degree-days for temperatures over 14.3 °C; therefore, at 30 °C, *Culex* mosquitos can transmit the virus in just 7 days after being exposed[72]. However, this comes at a cost, as the survival of the mosquito decreases as the temperature increases [62]. Transmission peaks at temperatures between 23 and 26 °C [73]. An increase in temperature has shown a positive association with the circulation of WNV in Southern Europe, with higher temperature lengthening the vector's season [27••].

Consequently, as global warming progresses, the rate at which *Culex* populations multiply and become infected with WNV may increase in temperate regions. Evidence of this is already present in the Americas, where increasing temperatures have permitted *Culex* species to expand northward, with *C. pipiens* reaching southern Canada [74]. In Southern Europe, this phenomenon has been observed with an increase in temperature, showing positive association with the circulation of WNV and lengthening the vector's season [27••]. In addition, changes in precipitation patterns will create additional habitats for these vectors, enabling them to colonize new areas and expand their populations [74].

Therefore, an integrative approach to address human, animal, and environmental health (One Health approach) will be critical to understanding and limiting the impact on humans. One such example is observing several birds, such as crows and jays succumb to WNV infection. This has led to the use of dead-bird surveillance programs to track WNV emergence and permit the preemptive allocation of mosquito control resources in areas of increased risk [75, 76].

Clinical Manifestations, Diagnosis, and Management

Clinical manifestations include asymptomatic infection, WN fever, or neuroinvasive disease (WNND). The majority of the patients (> 80%) remain asymptomatic, with only 1% of patients presenting with neurological manifestations [77].

In uncomplicated WN fever, most patients present with acute onset of fever, chills, nausea, weakness, fatigue, myalgia, arthralgia, and headache [77, 78]. Around –-50% of patients may develop lymphadenopathy associated with rash lasting approximately 7 day s[2, 6]. These symptoms are usually mild and resolve in less than a week, but prolonged fatigue is common [6]. Patients' history plays a vital role in diagnosing these cases, such as a history of travel to endemic regions, especially during the summer months, outdoor activities, mosquito bites, and other environmental conditions. A thorough physical examination is necessary to identify any rash, mosquito bite, or lymphadenopathy. Specific laboratory tests on serum and CSF are warranted to confirm the diagnosis. Serological tests include WNV-specific antibody tests on serum or CSF samples (IgM-specific ELISA) [77, 78]. In immunocompromised hosts, antibody development might be delayed. In such cases, PCR detection for WNV can be helpful. The plaque reduction neutralization test (PRNT) is the most specific antibody test for flaviviruses. To date, the mainstay of treatment for WNV infection is supportive care [2], which includes managing nausea and vomiting with antiemetic and rehydration, analgesics, and antipyretics.

In rare and severe cases, patients have neurological manifestations leading to WNND. WNND includes syndromes of meningitis, encephalitis, acute flaccid paralysis (AFP)/poliomyelitis, and transverse myelitis [77, 79]. In rare cases, cranial nerve palsies, movement disorders, and parkinsonian features have also been reported [79]. The exact mechanism of neuro-invasion is unclear. Possibly, an overactive immune response leads to increased permeability of the BBB to the virus; however, if the immune system lags in clearing the virus, neuronal cell death can occur, associated with severe manifestations [7]. Risk factors for encephalitis include older age, diabetes, alcohol abuse, and immunocompromised states [80]. Amongst neuroinvasive cases in the USA, hospitalization rates were > 85% in all age groups but were highest among patients aged ≥ 70 years (98%) [35]. Clinical and laboratory evaluation, along with neuro-imaging, play a pivotal role in diagnosing these cases. Patients frequently have an altered mental status, cranial nerve abnormalities, and generalized weakness. In patients with AFP, asymmetric lower motor neuron weakness with preserved sensations and abnormal deep tendon reflexes might be noted [79]. Laboratory investigations on serum samples mainly reveal leukocytosis, anemia, hyponatremia, transaminitis, and rarely elevated creatinine kinase levels. CSF studies show neutrophil predominant pleocytosis and elevated protein levels, and the serological and viral tests are crucial in confirming these cases.

Despite the relative insensitivity, with only 20 to 70% of patients with acute WNND having associated abnormalities, MRI is the key study in neuro-imaging [77]. When present, lesions preferentially affect deep gray matter structures, including the basal ganglia, thalami, brainstem, and cerebellum [79]. In the case of AFP, MRI can sometimes show abnormalities in the anterior horns. However, electrophysiological studies (electromyography and nerve conduction velocities) can help in further characterization [79].

Management for WNND is symptomatic with supportive care. Patients at risk of airway compromise require urgent intubation and ventilation support. Even though a small randomized control trial of 18 patients did not show any significant benefits from high-dose corticosteroids [81], several case reports with neurological manifestations observed clinical improvement [8, 9]. Animal models have also shown potential benefits with IVIG [82, 83] but a randomized clinical trial failed to show any benefits in humans [84]. Similarly, in vitro studies have shown promising results for interferon and ribavirin [85, 86]. However, these compounds have shown mixed evidence when used in humans [2, 87, 88]. There is also some ongoing research for newer therapeutics [89•]. Patients with WNND, especially those with AFP, require long-term acute rehabilitation and physiotherapy [2, 77]. Long-term complications for a year or more after infections are common in patients recovering from WNV infection.

Travel-Related WNV—Case Compilation

Our PubMed search identified 39 reports of travel-related WNV infection in published literature[90]. (Table 2 and Fig. 1). Of these 39 cases, eighteen were reported from East and Southeast Europe, eight from Eastern Mediterranean and North Africa, seven from Sub-Saharan Africa including Madagascar, five from North America, and one from Central America. Nearly all travelers (35) were from Europe. Socio-demographic and past medical history was available in 25 cases. In these 25 cases, the age range varied from 23 to 83 years, with 10 patients (40%) having an age of ≥ 65 years. Five patients reported a current or past history of immunosuppression (4 patients had a history of cancer, and 1 patient had a renal transplant). Most of these patients (19/29 cases with details available, 65.5%) were reported to have neurologic involvement. An adverse outcome, such as death, neurological sequela, or prolonged recovery was reported in 15 patients.

Discussion

The majority of imported WNV cases in our literature review manifested neurologic disease or severe disease, and a sizable proportion of cases were 65 years or older. The increased risk for severe disease in persons with advanced age or comorbidities calls for heightened caution for these populations when visiting endemic regions, especially in the months of high transmission [110, 111]. Since no antiviral is available to treat WNV infection, and no vaccine is available, prevention in travelers rests on avoiding bites by the vectors, primarily *Culex* mosquitoes. Wearing clothing such as long sleeves, trousers, and socks provides an essential layer of protection.

Furthermore, several public health measures have been deployed to limit the number of infections caused by the virus. One Health approaches, through surveillance of outbreaks in birds and horses act as early warning systems [4, 75, 76]. In addition, WNV has long been a reportable disease, which permits active surveillance data to be collected, leading to early recognition of outbreaks [112]. Lastly, the screening of donated blood for WNV acts both as a surveillance tool as well as a preventive measure, as blood products that test positive are discarded [113, 114].

The main vector mosquitoes *Culex* spp. are night biters and have peak biting activity at dusk and dawn. Travelers to WNV-endemic areas should be advised to apply EPA-approved repellent during peak biting activity times [115]. An additional bite prevention strategy is to treat outer clothing with permethrin (or another pyrethroid) when traveling in an area with a high incidence of WNV [116]. Similar to other vector-borne diseases, insecticide-resistant genes

Table 2 Published reports of West Nile virus in travelers

Year of occurrence	Patient, significant PMH	Origin/residence country	Destination	Reason for travel	Duration and city of stay in the endemic areas	Lineage	Clinical course and outcome
2001 [90] (Estiva et al.)	41-year-old female, previously healthy	France	Senegal	Tourism	NA	NA	Acute febrile rash, rapid recovery as inpatient
2001 [10] (Meeuse et al.)	45-year-old female, previously healthy	The Netherlands	Israel	Tourism	NA	NA	Fever and altered behavior, rapid recovery as inpatient
2002 [91] (Hubalek et al.)	69-year-old male, previously healthy	Czech Republic	USA	Tourism	2-month trip	NA	Fever, blurred speech, marked bradypsychism, and hydrocephalus, gradual recovery
2003 [92] (Charles et al.)	82-year-old male	France	USA	Tourism	Atlanta, Georgia,	NA	Encephalitis, inpatient rapid recovery
2003 [93] (Prick et al.)	69-year-old male	The Netherlands	Canada	Tourism	Ontario	NA	Encephalitis, rapid recovery as inpatient with a residual short-term memory dysfunction
2007 [94] (D VDB et al.)	NA	Belgium	USA	NA	Florida	NA	Neuroinvasive disease
2008 [94] (D VDB et al.)	NA	Belgium	Senegal/Guinea	NA	NA	NA	Confirmed WNV fever case without neuro involvement
2008 [95] (Monge Maillo B et al.)	51-year-old, previously healthy male	Spain	Nicaragua	Missionary	2-year stay in Managua	NA	Meningo-encephalitis with acute flaccid paralysis, residual right upper limb paraparesis and muscular atrophy
2009 [96] (Rogers et al.)	58-year-old male	Australia	Israel	Visiting friends and relatives	Tel Aviv	1 (New York 99 strain)	Encephalitis, rehabilitation for persisting lethargy and mild ataxia
2010 [97] (Aboutaleb et al.)	30-year-old female, previously healthy	Germany	Israel	Tourism	10-day trip at the Sea of Galilee	NA	Fever, retro-orbital headache, and a macular rash, inpatient rapid recovery
2011 [98] (Schultze-Amberger et al.)	28-year-old female, previously healthy	Germany	Canada	Tourism	2-week holiday trip to Ottawa mainly, and Ontario	NA	Severe encephalitic syndrome, discharged after 2 months in a rehabilitation center with full recovery
2011 [99] (Larrieu et al.)	58-year-old female, history of hypertension	Reunion island	Madagascar	Tourism	2 weeks in the province of Mitsinjo	NA	Encephalitis, death after 1 month due to cardiogenic shock
2012 [100] (Kropman et al.)	44-year-old female	The Netherlands	Egypt	Tourism	NA	NA	Poliomyelitis-like, lower extremity weakness/paralysis, with complete recovery on the right and partial recovery on the left
2012 [101] (Gabriel et al.)	65-year-old male, history of reduced cardiac output (ejection fraction 25%), coronary artery bypass graft surgery in 1990, and an implantable cardioverter-defibrillator several years ago	Germany	Greece	Tourism	several weeks in the village of Leskimi in Corfu	NA	Neuroinvasive disease, impaired motor and cognitive capacity, death after 3 months of neurological rehabilitation due to septic shock
2012 [102] (Cnops et al.)	73-year-old female, history of lymphoma	Belgium	Greece	Tourism	Kavala city in Macedonia	2	Encephalitis, death
2012 [94] (D VDB et al.)	NA	Belgium	Democratic Republic of Congo	NA	NA	NA	Neuroinvasive disease present
2012 [94] (D VDB et al.)	NA	Belgium	Sudan	NA	NA	NA	WNV fever without neuroinvasive disease

Table 2 (continued)

| Year of occurrence	Patient, significant PMH	Origin/residence country	Destination	Reason for travel	Duration and city of stay in the endemic areas	Lineage	Clinical course and outcome
2012 [101] (Gabriel et al.)	60-year-old male, history of kidney transplantation in 1999 due to nephrosclerosis	Germany	Montenegro	Tourism	Bijela, and traveled back by road, via Bosnia, Serbia, and Hungary	NA	Neuroinvasive disease with several complications including seizures, kidney transplant failure, and gastrointestinal bleeding. Severe residual speech and motor impairment
2012 [101] (Gabriel et al.)	23-year-old female, previously healthy	Germany	Egypt	Study	7 months in Cairo	NA	Influenza-like illness, inpatient rapid recovery
2012 [101] (Gabriel et al.)	43-year-old male, previously healthy	Germany	Tunisia	Tourism	NA	NA	Fever, asthenia, and hematemesis, inpatient rapid recovery
2012 [103] (Hwang et al.)	58-year-old male, medical history of diabetes and tobacco smoking	Korea (first reported case of WNV in Korea)	Guinea	Business trip	Was in Guinea, West Africa 7 months ago	NA	Headache since 2 months, cognitive impairment with mild memory disturbance, Leg weakness, arachnoiditis, myelitis
2013 [104] (Quatresous et al.)	74-year-old male, history of hypercholesterolemia and asymptomatic carotid stenosis,	France	Algeria	Tourism	NA	NA	Orchi-epididymitis and meningo-encephalitis
2015 [105] (Pietsch et al.)	34-year-old female, previously healthy	Germany	Austria	Tourism	4-week trip to the Barrier Lake of Ottenstein and Vienna	2	Influenza-like illness and exanthema, outpatient, rapid recovery
2016 [106] (Paphitou et al.)	75-year-old male, history of coronary artery disease and localized prostate cancer	Cyprus	Greece	Tourism	NA	NA	Meningo-encephalitis and flaccid paralysis, successfully weaned from mechanical ventilation and able to move his limps against resistance on day 60 of rehabilitation
2017 [11] (Parkash et al.)	72-year-old male, CKD stage 3	UK	South Africa	Visiting friends and relatives	3-week in Johannesburg, except for a 5-day safari in Kruger National Park region	2	Influenza-like illness, inpatient rapid recovery
2017 [107] (Wollants et al.)	83-year-old male, history of moderate chronic kidney disease	Belgium	Hungary	NA	8-month trip	2	Multiple organ failure and loss of consciousness, residual memory loss 3 months after rehabilitation
2017 [11] (Prakash et al.)	76-year-old female, previously healthy	UK	South Africa	Visiting friends and relatives	3-week in Johannesburg, except for a 5-day safari in Kruger National Park region	2	Meningo-encephalitis, residual mild cognitive impairment, ongoing balance disorder
2018 [108] (Velasco et al.)	60-year-old male, history of meningioma (treated with radiotherapy years ago) and thymoma in clinical remission	Spain	Romania	NA	Ajdud	2	Neuroinvasive disease, acalculous cholecystitis, pancreatitis, Takotsubo syndrome, full recovery after 1 year of rehabilitation
2018 [28] (Nagy et al.)	10 imported cases noted in Hungary	Cases were related to travel to following countries: Austria (1), Belgium (1), Croatia (2), Romania (2), Serbia (1 confirmed, 2 probable), Turkey (1)					
2019 [109] (Whyler et al.)	63-year-old female, history of follicular lymphoma in remission, with rituximab-induced hypogammaglobulinemia	Australia	Southeast Europe	Tourism	2-month travel to Danube River, Serbia, Croatia, Germany, Austria, Slovakia, and Hungary	2 (West Nile virus Bulgaria 2015)	Meningo-encephalitis with severe acquired brain injury, death after 32 days
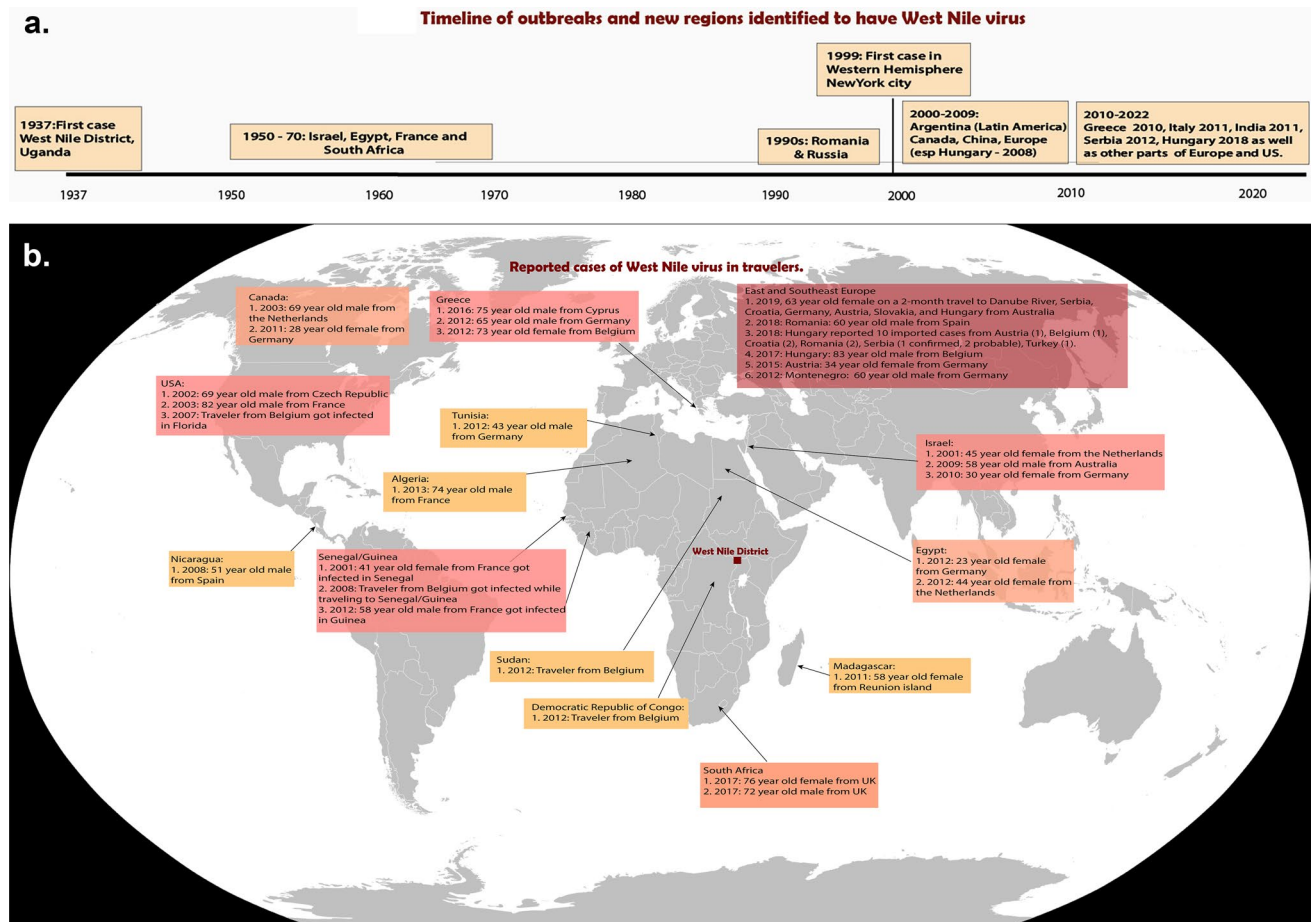
Fig. 1 **a** Timeline of outbreaks and new regions identified to have West Nile virus. **b** Reported cases of West Nile virus in travelers (area of acquisition)

have been identified in *Culex* mosquitoes and appear to be associated with enhanced vector competence for WNV [117]. Travelers likely need to use multiple bite prevention measures to reduce the risk of WNV infection. Mosquito avoidance strategies still need improvement since the vector avoidance practice by travelers to malaria-infested regions remains suboptimal despite receiving advice and educational material by healthcare professionals prior to travel [118].

Despite WNV-focused mosquito surveillance and control efforts such as insecticide spraying undertaken by health authorities, forecasting human WNV risk level at destinations remains challenging due to the complex interactions between the virus, the reservoir hosts, mosquito vectors, and environmental factors such as temperature, precipitation, population density, immunity, and land use. [119••, 120] The exposure destinations from our case reviews were widely distributed and included most of the known areas with WNV activity. In regions with suboptimal WNV surveillance, such as Africa, travel-related WNV infections may serve as sentinels of virus circulation [121].

While our review sought reports on patients that acquired WNV infection at their travel destination, travelers from a WNV-endemic area can also import the infection to their destination. For instance, a 59-year-old male traveler from Philadelphia, the USA, to London, UK, developed confusion, and serology and MRI imaging were consistent with his diagnosis of neuroinvasive WNV[122]. Although *Culex* mosquitoes have been detected in the UK, this case, fortunately, did not lead to further spread.

As the global spread of the WNV continues, the need for the development of an effective vaccine is increasing. Despite several vaccines being available for horses, a suitable human vaccine is yet to be approved [123]. However, there are currently multiple human vaccines candidates in development, with some entering phase II trials [124]. Furthermore, in vivo studies have shown that there is some degree of cross protection against WNV in animals that have been immunized against other flaviviruses, such as Japanese encephalitis virus. It remains to be determined whether such an effect is observed in humans as well [125]. Continued research in developing an effective human vaccine will be essential to prevent future outbreaks.

Limitations

Several limitations are present in this review. A systemic search of gray literature was not conducted. While some cases can be identified as an imported cases based on travel history and endemicity of the region (e.g., ex. Korea), many imported WNV infections may be under-recognized due to the wide geographic distribution of WNV. In areas known to have WNV, confirmation of an imported case may be difficult unless molecular characterization can be performed [126, 127]. Furthermore, mild cases may not undergo testing for specific diagnosis if patients recover quickly; therefore, the published travel-related cases may be biased towards a high prevalence of neuroinvasive manifestations.

Conclusion

WNV is an emerging arbovirus that can cause disease ranging from asymptomatic to devastating. Because the presence of its vectors is increasingly identified, cases of WNV disease will likely be reported from new areas. Improved surveillance is needed in many regions. Travelers are potentially at risk, especially if they are unaware of the presence of competent mosquitoes at their destination. Health care providers should advise their patients planning to travel to endemic areas regarding WNV risk and mosquito bite prevention methods. Evaluation of ill travelers with compatible symptoms should consider the diagnosis of WNV for those visiting in endemic areas as well as for those returning from destinations with known WNV circulation.

Compliance with Ethical Standards

Ethics Approval This review article is in compliance with ethical standards.

Conflict of Interest Chinmay Jani, Loukas Kakoullis, Nour Abdallah, Christian Mouchati, Stephanie Page, and Robert Colgrove report no conflict of interest. Lin Chen reports honoraria from Shoreland Inc, Valneva Inc, Takeda, Sanofi-Pasteur, Emergent BioSolutions, and Merck, not related to this work.

Research Involving Human and Animal Participants This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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