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Review Article

Effects of climate change on vector-borne diseases: an updated focus on West Nile virus in humans

Shlomit Paz

Department of Geography and Environmental Studies, University of Haifa, Haifa, Israel

Correspondence: Shlomit Paz (shlomit@geo.haifa.ac.il)

One of the main impacts of climate change on health is the influence on vector-borne diseases (VBDs). During the last few years, yearly outbreaks of the West Nile virus (WNV) have occurred in many locations, providing evidence of ongoing transmission. Currently, it is the most widely distributed arbovirus in the world. Increases in ambient temperature have impacts on WNV transmission. Indeed, clear associations were found between warm conditions and WNV outbreaks in various areas. The impact of changes in rainfall patterns on the incidence of the disease is influenced by the amount of precipitation (increased rainfall, floods or droughts), depending on the local conditions and the differences in the ecology and sensitivity of the species of mosquito. Predictions indicate that for WNV, increased warming will result in latitudinal and altitudinal expansions of regions climatically suitable for transmission, particularly along the current edges of its transmission areas. Extension of the transmission season is also predicted. As models show that the current climate change trends are expected to continue, it is important to reinforce WNV control efforts and increase the resilience of population health. For a better preparedness, any assessment of future transmission of WNV should consider the impacts of the changing climate.

Introduction

Climate change impacts on vector-borne diseases

Climate change is the greatest challenge of the 21st century, threatening all aspects of human society including increasing risks to human life and health [1]. It impacts directly through extreme heat, cold, drought or storms, or indirectly by changes in water availability, food provision and quality, air pollution and other stressors. Most climate-related health impacts are mediated by complex ecological and social processes, while the impacts vary in magnitude and timing as a function of the local environmental conditions and the vulnerability of the human population [2–4].

One of the main impacts of climate change on health is the influence on vector-borne diseases (VBDs) transmission since a warmer climate and changing rainfall patterns may create hospitable environments for mosquitoes, ticks, and other climate-sensitive vectors [3]. Long-term anthropogenic climate change interacts with natural variability, influencing the transmission of VBDs from shorter (seasonal, annual) to longer (decadal) time scales, with variable effects and complex interactions at different times and locations. These influences may reinforce one another [5]. The impacts of climate are potentially complex and further complicated by nonlinear feedbacks inherent in the dynamics of many infections, driven by the processes of immunity and transmission [6]. Although the climate is one of several factors that influence the distribution of VBDs, it is well known as a major environmental driver influencing their complex epidemiology [7,8].

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Infectious VBDs are mainly transmitted by arthropod vectors, which are particularly sensitive to changes in climate. Arthropods are ectothermic and their internal temperature is regulated by external environmental conditions. Their larval development stage generally requires the presence of bodies of water and/or specific humidity conditions. Weather conditions, in particular temperature, precipitation and humidity, affect the survival and reproduction rates of the disease vectors (mosquitoes, in most cases), their habitat suitability, distribution and abundance [8–11]. Temperature affects the rate of pathogen maturation and replication in mosquitoes, impacts the density of insects and increases the likelihood of infection. Upsurges in temperature can reduce the period of the pathogens' incubation and life cycle of vectors, thus boosting transmission risk through elevated vector populations within a certain temperature envelope. In addition, vector biting rates tend to increase with a rise in temperature [7–12].

Precipitation also exerts a strong influence on VBDs dynamics, mostly in the case of diseases transmitted by vectors (such as mosquitoes) that have aquatic developmental stages but also via humidity on diseases transmitted by vectors without such stages, such as ticks or sandflies [5].

West Nile virus

The West Nile virus (WNV) is one of more than 70 viruses of the family *Flaviviridae* of the genus *Flavivirus*. Serologically, it is a member of the Japanese encephalitis serocomplex [13,14]. Although most people (8 out of 10) infected with WNV do not develop any symptoms, infections can be serious, mainly among the elderly. About 1 in 150 people who are infected, develop a severe illness affecting the central nervous system such as encephalitis or meningitis [14,15]. Although infrequent, infections can also be acquired through contaminated substances of human origin (such as donated blood, transplants) [14,16]. When humans are infected with WNV, the immune system is rapidly engaged and drives antiviral immune responses necessary for controlling virus replication, limiting virus-mediated pathology, and providing immunity against re-infection [17]. Currently, no vaccine or specific antiviral treatments for WNV infection are available [15].

The virus circulates in a sylvatic/rural cycle between birds and ornithophilic mosquitoes, particularly members of the genus *Culex*. Under certain environmental conditions, it spreads to human settlements where it infects humans and equines and may cause large epidemics [18]. The transmission cycle exists in rural ecosystems as well as in urban areas [8] while the distribution of WNV is dependent on the occurrence of susceptible avian reservoir hosts and competent mosquito vectors, mosquito host preference and availability of hosts [13].

Native mosquitoes' feeding behavior, presence of susceptible endemic birds and local environmental conditions are essential for persistence and amplification of the virus while infected migratory birds are responsible for the introduction of the virus in new areas [19]. Outbreaks of WNV infection are highly sporadic and focal in nature, exhibiting high variability in their development and incidence across different regions [20].

WNV has been circulating in Africa since 1937, and, up until the early 1990s, human outbreaks have been reported in Africa and Israel, mainly associated with mild febrile illnesses. Since then, new viral strains, probably of African origin, have increased human disease incidence in parts of Eurasia with large outbreaks of increased clinical severity [13,21]. Starting in 2010, there have been yearly outbreaks of WNV in eastern and southern Europe, providing evidence of ongoing transmission [22]. The first domestically acquired human cases of WNV disease in the Western Hemisphere were detected in New York City in 1999 [23]. In the years that followed, WNV rapidly spread, and by 2005, it had established sustained transmission foci in much of the hemisphere with an overall distribution that extended from central Canada to southern Argentina [24]. Since then, WNV remains the leading cause of domestically acquired mosquito-borne disease in North America [25] and currently, it is the most widely distributed arbovirus in the world, occurring on all continents except Antarctica [26].

Impacts of climate change on WNV transmission

Among the factors that affect the complex epidemiology of WNV, weather conditions, especially temperature and precipitation, have direct and indirect influences on the life cycles and competence of mosquitos, on their population dynamics and on the virus replication rate of the mosquito [22,27]. These influences, often in complex and nonlinear mode [28] on the vector, virus and hosts, and on the interactions between them [18], are intensified under conditions of extreme weather events such as heat waves, floods or drought, resulting from climate change [8].

An increase in ambient temperature causes an upsurge in the growth rates of mosquito populations, a decrease in the interval between blood meals and a shortening in the incubation time in mosquitoes. Although in some cases, extremely high temperatures begin to slow down mosquito activity [29,30], in general, the replication cycle is completed more quickly in mosquitos at higher temperatures [31] which accelerates the virus evolution rate and increases the viral transmission efficiency to birds. Outbreaks emerge when adequate amplification in the bird population occurs early in the summer months with sustained above average daily temperatures [32].

Clear associations have been found during the past few years between warm conditions and WNV outbreaks in various locations. In Europe, July temperature anomalies were detected as a predictor of WNV risk in humans later in the season [33]. Positive lag correlations were observed for southern and eastern Europe between the number of WNV cases in humans and temperatures, with a geographic latitude gradient of increased weeks' lag, towards the colder countries [34]. In northern Italy, high temperatures have been associated with the incidence of WNV infection after a lag of 5–6 weeks [35]. A study in the Danube Delta, Romania, showed that the early rise of temperature contributed to the increase in mosquito population size and accelerated the transmission of WNV in the vectors in the weeks that followed [36].

National and regional models for the U.S.A. revealed that higher than average temperatures in the months preceding a WNV season were associated with an increased risk of higher than average disease incidence [37]. In Connecticut, statistical linkage was found between warm conditions and higher human infection risk [38]. In Georgia, U.S.A., the temperature was found to be among the most important variables in predicting WNV distribution [39].

In a colder climate, in Ontario, Canada, a moderate to strong correlation was identified between temperature and minimum infection rate with a 4–5 lag period. These lags are consistent with established timelines of larval development, adult feeding preparation, ovarian development, and a viral incubation period [40]. Another study in Ontario showed that higher winter minimum temperatures were also strongly associated with annual WNV incidence [41].

The establishment of WNV in new regions is facilitated by warmer conditions [8]. In an area where the process of endemization has recently started, WNV is known as climate-sensitive [35]. An example is the recurring annual outbreaks, occurring in eastern and southern Europe every summer (2011–2018) since the unprecedented outbreak in 2010 which was accelerated by extreme temperatures [34]. These annual epidemics of WNV provide evidence of ongoing transmission in Europe [16,22,42].

Precipitation is the source of water for many mosquito breeding habitats. However, the effects of precipitation on WNV vector populations is difficult to capture in linear models [43]. The impact of changes in rainfall patterns on the response of disease incidence is influenced by the amount of precipitation (increased rainfall, floods or droughts), depending on the local conditions and the differences in the ecology and sensitivity of mosquito species [8,44]. Rainfall increases near-surface humidity, which enhances mosquito flight activity and host-seeking behavior and alters the abundance and type of aquatic habitats available to the mosquito for egg deposition and sub-adult growth [45]. Heavy rainfall increases the standing water surface which is necessary for mosquito larval development. For instance, in northern Italy, heavy precipitation has been associated with the incidence of WNV infection after a lag of 2–3 weeks [35]. On the other hand, heavy rains can also disturb breeding habitats and decrease vector populations by flushing the ditches and drainage channels used by *Culex* larvae, wash away eggs and larvae and dilute the nutrients for the larvae, and consequently decrease the development rate [12,46].

Drought conditions can facilitate population outbreaks of some species of mosquitoes since the drying up of wetlands disrupts the aquatic food–web interactions that limit larval mosquito populations [47]. When precipitation amount decrease, standing water pools become richer in the organic material that mosquitoes need to thrive [36]. Such drying wetlands and water supplies used by humans attract several bird species and increases the bird–mosquito interaction which accelerates the epizootic cycling and amplification of WNV within these populations [3,8]. Moreover, it was found that drought conditions can facilitate population outbreaks of some species of mosquitoes in the following year [47].

In a study on the transmission dynamics of WNV in mosquito populations in the wetland ecosystem of the Danube Delta, Romania, significant negative linkages were detected between a decrease in precipitation amounts and an increase in infection rate in mosquitoes. The heat and drought conditions led to a shrinking of the water bodies and, therefore, the organic matter became more concentrated (eutrophication) [36]. Such conditions favor the *Culex pipiens* species and are also attractive to several bird species [8]. Drought and immunity were found as primary drivers of inter-annual variation in WNV across the U.S.A. It was noted that increases in drought could potentially double WNV epidemic intensity nationally, with epidemics in areas of low immunity being even larger [48].

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Table 1. Main direct impacts of climate change on the epidemiology of WNV

Parameter	Main influences	Comments
Increase in temperature	• Upsurge in the growth rates of mosquito populations • Decreases in the interval between blood meals • Shortening of the incubation time in mosquitoes • Speeding up the virus replication cycle	Positive associations between warming and WNV transmission were detected in areas with different climatic–environmental conditions (e.g. Mediterranean Basin, Eastern Europe, and North America)
Changes in rainfall patterns	*Increased rainfall, floods*: • Lead to higher mosquito abundance • Reduce potential by flushing drainage channels used by *Culex* larva *Drought*: • Stagnant water pools with richer organic material attract various species of mosquitoes and birds	Various impacts, probably resulting from the diversity of climatic types and environmental conditions of different locations, and the geographic differences in the primary WNV mosquito vectors
Increased relative humidity	Positively correlated with vector population dynamics	Association with WNV transmission is less significant than with temperature and precipitation

Across the U.S.A., the association between precipitation and WNV disease incidence varied regionally, which is partly explained by the diversity of WNV disease ecology in different regions as a result of different climatic types and geographic differences in the primary WNV mosquito vectors (e.g., *Cx. pipiens* in the northern U.S.A. and *Culex tarsalis* in the plains and Western states). Lower than average annual precipitation was associated with increased WNV disease in most of the U.S.A.'s eastern regions and the Northern Rockies and Plains, and higher than normal total precipitation was associated with increased WNV incidence in the Western regions [37]. In a study in West Texas, a correlation was found between wetter spring conditions combined with drier and cooler summer conditions and elevated human WNV infection risk [49]. Dry summer soil moisture conditions have been positively correlated with WNV prevalence in *Culex* mosquitoes in New York [50]. Similarly, positive relationships were found in Colorado between drought and WNV infection prevalence in mosquitoes. It was found that drought alters transmission not only by reducing mosquito abundance but also by increasing infection prevalence. Since increased aridity is projected in many regions of the U.S.A. [51,52], it is important to consider moisture availability and not only precipitation [48].

The impact of relative humidity on WNV eruption has been studied less. The research found that air temperature is a better predictor than air humidity for increasing cases of disease. For instance, in the Greater Tel Aviv (Israel) area, positive correlations were found between patients' hospital admission dates and relative humidity levels [53]. An association between average maximum relative humidity and vector population dynamics was detected in Maryland, U.S.A. [54], and correlations were also found between morbidity and weekly relative humidity in south-eastern Europe [34]. Linkages between lagged weather conditions and *Cx. pipiens* dynamics were analyzed in a study for eight functional units located in France, Greece, Italy and Serbia. Relative humidity was found to have a consistent effect on *Cx. pipiens* dynamics, although less strong than temperature and of opposite sign (i.e. a negative correlation at short time lags). Given the negative correlation between temperature and relative humidity, part of this was explained by variation in *Cx. pipiens* dynamics by relative humidity; and might be actually explained by temperature, or vice versa [55]. In a recent modeling study, measurements of atmospheric water-vapour were found to be better predictors of WNV cases than precipitation, soil moisture, and evapotranspiration [43].

The main direct impacts of climate change on the epidemiology of WNV are summarized in Table 1.

Other environmental drivers

VBD risks are dynamic and subject to multiple and complex drivers [16,56]. The complex epidemiology of WNV, its transmission and distribution, are impacted directly and indirectly by multiple factors besides

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weather conditions such as biodiversity loss and intense changes in land use [8]. Part of these non-weather drivers might be influenced by climate change such as fluctuations in bird migration patterns. In a study on environmental conditions that favor WNV outbreaks in Europe, irrigated croplands as well as highly fragmented forests were positively associated with disease cases [57]. Another study for Europe stressed the importance of water bodies in the risk of WNV transmission by showing that areas including wetlands with positive anomalies of the modified normalized difference water index (MNDWI) in June are more at risk [33].

Biodiversity loss may lead to an increase in the transmission of VBDs as WNV. Loss of biodiversity through climate change could affect competent reservoir hosts, which tend to thrive in species-poor communities. In such case, the vectors are more likely to feed upon these competent reservoirs and become infected. This dynamic might increase the risk of human disease [12,56].

Since birds are the principal hosts for WNV, increased temperatures might have an indirect effect on the virus spreading through impacts on bird populations and migratory routes. Warmer than normal winter temperatures may affect bird migration, hatching, or avian community composition [37]. A recent study on the population of European pied flycatchers (*Ficedula hypoleuca*) suggested that, together with the advancement of breeding and molt, birds are now departing earlier [58]. It was found that alterations in migration timing in association with temperature changes are occurring both in long- and short-distance migrants all over the U.S.A. [59]. Such changes may influence the appearance timing of the disease in locations near or along migration routes [8].

Socioeconomic factors and human behavior

Apart from their influence on the environment, humans are involved in affecting the transmission of VBDs which are sensitive to climate change, including WNV, in several ways. The impacts vary between regions as a result of differences at the demographic and socioeconomic levels [5]. Socioeconomic characteristics such as the age and density of the dwellings, income, education levels and ethnicity, were found to be correlated with WNV infection rates [60]. For example, in old houses, old sewerage systems and mature trees might be suitable for bird habitats [61]. Moreover, the conditions in minority neighborhoods, characterized by high rates of rental occupation, many vacant lots, poor drainage systems and lack of landscape upkeep could lead to increased mosquito habitats and consequently to higher WNV prevalence [62]. Populations living in poverty might be less likely to have secure, air-conditioned homes, and thus are more exposed to biting mosquitoes [22]. When the housing and infrastructures are poor, such as poor water supplies and drainage in settlements, the exposure to contaminated water which provides a habitat for mosquitoes leads to an increase in the disease incidence [12].

Human behavior has an impact on the sensibility to infection as well. For example, neglected swimming pools that provide mosquito breeding habitats or water-holding containers in the backyard may attract vectors. In addition, the use of personal protection is influenced by individual risk perception and may vary from year to year depending on public health education and media coverage [37,63,64].

In warm regions such as the Mediterranean Basin, as a part of the local mentality windows remain open for most of the hot months and many activities, particularly social gatherings, occur in outdoor locations such as shaded balconies and outdoor restaurants which are ideal for contact with the vector [65].

Another issue beyond climate change is the introduction of disease vectors by globalization, mainly through international trade and travel. A highly interconnected world may contribute to the generation of novel infectious disease risks [16]. For example, the large and increasing volume of air traffic into New York City over the past few decades makes the transport of infected mosquitoes on an airplane a likely pathway. Indeed, a close phylogenetic relationship between viruses isolated in New York in 1999 and those circulating in Israel in the previous year suggests a possible Middle East origin [66,67].

Prediction

Since seasonal WNV outbreaks vary considerably in size, location and scope, it is non-trivial to project future WNV activity from current or observed conditions [14,25] and even after an outbreak has begun, it remains difficult to predict the future characteristics of possible epidemics [68]. However, for a better preparedness and prevention in the near and distant future, attention should be paid to the impacts of the changing climate on future transmission of WNV.

The recent Special Report of IPCC (2018) focuses on the impacts of global warming of 1.5°C above pre-industrial levels. The report shows that a warming of 2°C poses greater risks to human health than one of 1.5°C, often with the risks varying regionally. There is high confidence that higher temperatures will affect the

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transmission of some VBDs (such as malaria, dengue fever and WNV), with increases and decreases in projections depending on the disease region and the degree of temperature change. The report indicates that for WNV, increased warming could result in latitudinal and altitudinal expansions of regions climatically suitable for WNV transmission, particularly along the current edges of its transmission areas, with an increase in the annual number of disease cases [69]. Additionally, an extension of the transmission season is predicted. A greater risk is projected with regard to global warming of 2.0°C than one of 1.5°C [70–73].

On a more regional basis, projections for Europe indicate a continuous extension of regions with an increased risk of WNV infections, mainly on the fringes of the regions of transmission. Predictions for 2025 show an elevated risk in north-east Greece, east Croatia and north-west Turkey while projections for 2050 show a further expansion of high-risk areas [16,72]. Currently, the temperature is an important limiting factor for WNV circulation in northern Europe, but modeled scenarios show that transmission cannot be ruled out [74].

A study used dynamics simulation model parameterized for three WNV vectors has estimated mosquito population dynamics under current and projected future climate scenarios for multiple locations across the U.S.A. The analysis indicated that changes in mosquito population dynamics will vary by location, while mosquito activity periods are generally expected to increase across sites in the northern latitudes of the U.S.A. [71]. Approximately, 590 additional West Nile neuro-invasive disease cases per year are predicted due to temperature increases by 2050 under the RCP4.5 scenario, with an impact of nearly \$0.5 billion. This represents an increase in ∼40% relative to the annual number of cases expected under baseline temperatures for a 2050 population [75].

Discussion

WNV in humans is a multi-factorial disease with a complex epidemiology. It is well known, however, that weather conditions have influences on the vector, virus and host, and on their interactions, and consequently on the transmission of the disease. This negative potential is intensified by the impacts of climate change which increase the frequency, intensity and severity of extreme weather events. Moreover, since the changing climatic conditions facilitate the establishment of WNV in new regions, processes of endemization have been documented in various locations, such as Europe and the U.S.A.

It is clear that higher temperatures accelerate the growth rates of mosquito populations and the replication cycle of the virus. This significant impact of warming on the eruption and transmission of the disease has been detected in areas with different climatic and environmental conditions, for example in the Mediterranean Basin, Eastern Europe and North America.

The linkage between WNV disease and precipitation amounts (such as heavy rainfall or drought) is more complex and varied regionally. For example, heavy rainfall increases the standing water surface which is necessary for mosquito larval development. On the other hand, when drought conditions cause a shrinking of water bodies, the organic matter becomes more concentrated and, therefore, attracts various species of *Cx. pipiens* and birds. The different impacts of rainfall patterns may be explained by the diversity of climatic types and environmental conditions of different locations and the geographic differences in the primary WNV mosquito vectors. Relative humidity was found to have an effect on mosquitoes' dynamics, although less significant than temperature and precipitation.

Apart from the direct impacts of weather parameters, other environmental changes made by humans, intensified by climate change (e.g. biodiversity loss, intense changes in land use, irrigated croplands, highly fragmented forests or over-extraction from water bodies) may negatively contribute to WNV dynamics and risks by, for instance, the effects of the changing conditions on the competent reservoir hosts.

Inadequate socioeconomic conditions are also known to be a risk factor for WNV upsurge. In poor neighborhoods, for instance, poor sewerage and drainage systems may be attractive for mosquito populations. When such conditions are favored by climatic changes such as severe heat waves and drought, the risk potential for WNV eruption may increase.

Over the last few years, projections that used modeling and dynamics simulations indicated a continuous extension of areas with an increased risk of WNV infections, mainly on the margins of the current regions of transmission. Despite these efforts, it remains challenging to predict the timing and scale of WNV in both endemic and new regions. Strengthening the public health preparedness for WNV eruptions is, therefore, a crucial adaptation strategy. Reinforcing WNV control efforts and population health resilience under the current and future impacts of climate change should include: monitoring and surveillance on a regular basis; risk assessment processes which are adapted to different climatic and environmental conditions as well as for populations in different socioeconomic levels; data and information sharing and collaboration between regions and

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countries; health system preparedness for possible outbreaks; and education that raises the public's awareness, particularly of mosquito bite prevention.

Summary

- It is known that recent climatic changes, particularly the increase in ambient temperature and fluctuation in rainfall patterns, have contributed to the endemization process of WNV in various locations.
- As predictions show that the current trends are expected to continue [76], health authorities responsible for VBDs control need to consider the scale and nature of the risks that climate change may encourage, by focusing on disease and location.
- It is important to reinforce WNV control efforts and increase the resilience of population health by monitoring and surveillance, environmental and vector management, health system preparedness, public education, evaluation and assessment, all by trans-disciplinary work and cooperation between countries since mosquitoes may spread easily across political borders toward populated areas.
- As climatic parameters are useful for detecting areas and periods of the year potentially characterized by a higher incidence of WNV infection, for a better preparedness, any assessment of future transmission of WNV should consider the impacts of the changing climate.

Abbreviations

MNDWI, modified normalized difference water index; VBDs, vector-borne diseases; WNV, West Nile virus.

Competing Interests

The Author declares that there are no competing interests associated with this manuscript.

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