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REVIEW

West Nile virus eco-epidemiology and climate change

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Abstract

West Nile virus (WNV) is an arbovirus with a wide geographical distribution. It is maintained in an enzootic bird-mosquito cycle and exhibits regular zoonotic transmission to humans, to whom it can cause West Nile fever and neuroinvasive disease. Over the last decades, WNV has emerged as a serious health threat with profound impacts on animal and human health. It is broadly accepted that climate change impacts the transmission of WNV through multiple pathways via its impacts on vectors, the pathogen, hosts, and the environment. Although some clarity has been established, the outcomes of these climate-driven processes are yet to be better understood before they can fully benefit tailored prevention and control measures. This review focuses on the eco-epidemiology of WNV and how it is impacted by climate change through an integrative lens. We discuss the role of eco-epidemiological modeling in knowledge generation and highlight the importance of adopting an interdisciplinary and transdisciplinary One Health approach for improved surveillance, data collection, modeling, and translation of outcomes into actionable policy and control.

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Introduction

West Nile virus (WNV) is a zoonotic arthropod-borne flavivirus from the Japanese encephalitis serogroup complex. The ecology of WNV is complex involving several virus reservoirs, arthropod vectors, and incidental or final hosts. Virus transmission to vertebrate hosts primarily occurs through bites of infected mosquitoes, which in turn can become infected when they feed on infected hosts. Wild birds have been identified as the main reservoir of WNV [1]. In endemic areas the enzootic cycle is maintained between ornithophilic mosquitoes and birds, although direct transmission between birds has been documented in laboratory and farm settings [2]. Many wild bird species that act as WNV reservoirs do not show clinical signs of infection. However, some species are highly susceptible to developing disease and significant bird population declines due to WNV outbreaks have been observed, particularly in North American species [3]. Humans, equids, and other mammals act as final or dead-end hosts of WNV as they do not produce sufficient levels of viraemia to transmit the pathogen back to the vectors. However, even though infections cannot be sustained between mammal hosts, WNV can have detrimental consequences on their health and severe economic impacts. Most humans that become infected with WNV do not present any signs of illness. However, about 25% of infections develop into West Nile fever (WNF) greatly varying in severity and less than 1% develop into neuroinvasive disease. Among the latter, approximately 10% result in death [1]. Around 20% of infected horses present clinical signs [4] and approximately 8% will develop severe WNV disease with neurological symptoms. Within diseased animals, fatality rate has been observed between 22 and 44% [5]. Upon infection with WNV, both humans and horses generate a humoral response characterized by the production of WNV-specific antibodies [6–8]. However, the duration of protection from reinfection or severe disease is not yet fully understood. Given the burden of WNV in these species, great efforts have been made to prevent the disease, including the development of prophylactic and therapeutic drugs. At present, there are six licensed vaccines to use in horses, contributing greatly to reducing the incidence of the disease [9]. However, human vaccines are currently still not available, mainly due to the lack of clinically advanced product candidates and concerns about cross-immunity challenges [10].

WNV was first isolated from a human in the West Nile district in Uganda in 1937 [11]. Until the early 1990s, WNV was associated with sporadic cases and outbreaks in Africa, Eurasia, Australia, and the Middle East [12]. In 1996, there was an apparent shift in its epidemiology, when human outbreaks became more frequent and the incidence of cases presenting severe disease increased throughout the Middle East and Europe [13]. Since then, Europe has witnessed a continued expansion in the areas affected by WNV and an upsurging trend in cases marked by major outbreaks in 2010 and 2018 [14, 15]. In 1999, WNV was reported in North America for the first time and rapidly spread across the continent, eventually reaching Central and South America [16]. Now, the virus is considered endemic in many parts of the world and regularly leads to outbreaks in these areas. In the USA alone, since the first incursion of WNV into the country, more than 51,000 human clinical cases have been reported, including over 2,300 deaths. Based on these numbers, it is estimated that 7 million people have been infected [17]. Although WNV is primarily vector-borne in the zoonotic cycle, transmission through infected blood or organ donation has been documented [18], as well as a case of transplacental contamination [19]. Despite its relatively low virulence in human hosts, WNV is now considered to have the widest geographic distribution and the largest range of vector and host species among all vector-borne flaviviruses, representing an ongoing risk to global health [20].

Mean global temperature has risen 1.2˚C above pre-industrial levels resulting in impacts on human, animal, and environmental health that include changes in infectious disease epidemiology [21]. It has become evident that the recent variations in climatic conditions have contributed to the endemization and suitability of WNV in various locations around the world [22, 23]. The relation between climate and WNV transmission has been excellently reviewed in a series of previous articles [14, 22, 23]. Here we review important aspects of WNV epidemiology at the vector and host level and major known effects of climatic conditions on both levels complementing these studies with a wider holistic One Health perspective. We focus specifically on the understanding and knowledge needs in relation to WNV and climate change and the role of eco-epidemiological modeling in this knowledge generation for improved policy and decision-making.

Vectors and climate

WNV can be transmitted by a wide range of mosquito vectors. However, only a few mosquito species from the genus *Culex* (*Cx.*) are considered the primary vector and are accepted to sustain transmission of the virus globally (Table 1) [2, 24, 25]. Females of some mosquito species

Table 1. Important vectors of WNV within the *Cx.* genus per world region.

World region	*Cx.* species
Africa	*Cx. univittatus*, *Cx. pipiens*, *Cx. tritaeniorhynchus*, *Cx. antennatus*, *Cx. theileri*, *Cx. neavei*, *Cx. poicilipes and Cx. quinquefasciatus*
Americas	*Cx. pipiens*, *Cx. quinquefasciatus* and *Cx. tarsalis*
Asia	*Cx. vishnui*, *Cx. fatigans (Cx. quinquefasciatus)*, *Cx. tritaeniorhynchus*, *Cx. bitaeniorhynchus*, and *Cx. univittatus*
Europe	*Cx. pipiens*, *Cx. modestus*, *Cx. molestus*, and *Cx. torrentium*
Middle East	*Cx. pipiens* and *Cx. perexiguus*
Oceania	*Cx. annulirostris*

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need to take a vertebrate blood meal to produce eggs [25]. This is when mosquitoes can become infected and transmit pathogens. The role of individual vector species in WNV transmission and amplification is determined by various factors including their vector competence, biting behavior, and abundance. Vector competence describes the inherent ability of mosquito vectors to be infected by, replicate, and transmit the virus, which is highly variable among and within species [16, 26]. The time it takes from a vector's exposure to the onset of its infectiousness is known as the extrinsic incubation period (EIP). Both the EIP and vector competence may depend on the viral variant the vector is exposed to [27–29].

Although some *Cx.* mosquitoes have been classified historically as ornithophilic, being able to maintain the enzootic cycle of WNV, they are now recognized as important bridge vectors, driving spillover to humans [30–32]. An overlap of *Cx. pipiens* and *Cx. restuans*, for example, seems to represent a high risk for spillover from birds to humans. This was observed in the northeastern United States due to high WNV prevalence and abundance of this species-pair, compensating for their predominantly bird-biting behavior [33]. By influencing host-vector contact rates mosquito feeding behavior plays a critical role in WNV transmission. Usually, mosquitoes have a preference to feed upon certain hosts, but their feeding patterns also result from host abundance and behavior such that vectors may feed upon certain species opportunistically when preferred ones are unavailable [34, 35]. It has been observed that mosquito biting behavior varies within the *Cx.* genus, geographically, and seasonally [30, 34, 36–40]. For example, an American study reported a particular shift of *Cx. pipiens and Cx. tarsalis* to feed on humans during late summer synchronized with dispersion and migration of their preferred host (American robins) and associated with amplification of human outbreaks [38]. Although observed at multiple sites this pattern seems not to be universal as indicated by studies in other regions of the USA that didn't find a late summer feeding shift to humans. In such regions human infection risk might still intensify during late summer simply related to a high amplification of virus during this period [30] or it might diminish when mosquitoes shift to feed on less competent avian hosts [39].

Cx. vectors breed in standing-water and are considered quite ubiquitous as they are observed in both urban and rural settings. Some species are abundant outside of cities, like *Cx. modestus* which mainly breed in brackish marshes and flooded rice-fields [41] or *Cx. tarsalis* which prefer sunlit standing water, like in savannas or grasslands [42]. Mosquitoes from the *Cx. pipiens* complex thrive in aquatic habitats rich in organic content. Such habitat is often generated near human settlements or farms (e.g., in containers, storm sewers, ditches). High human population density near these "man-made" mosquito habitats indicates an increased risk for spillover of WNV. The predominantly mammal biting *Cx. pipiens* form *molestus* even develops in highly polluted water environments and mates in confined spaces, making it a perfect "domestic" mosquito [31]. In Northern temperate regions this form has adapted to anthropogenic below-ground environments where it remains viable and active year-round [43]. Where closely related vectors co-occur, they can give rise to hybrid populations which may present their very own characteristics [40, 43, 44].

The recent environmental changes impact species' populations of vectors which manifests in altered abundance, range, and biting season. Despite their already broad distribution, *Cx.* mosquitoes have increased their geographical range and are projected to keep expanding to higher latitudes, also lengthening their activity season, and increasing their abundance in some regions [45–48]. In areas where temperatures will reach higher points than those ideal for mosquitoes, mortality is expected to increase, lowering vector abundance, especially during hot summers. Altitude is closely tied to environmental conditions like temperature, creating distinct ecological niches along altitudinal gradients. For example, in some regions of sub-Saharan Africa, *Cx. pipiens* seems to be confined to higher elevations, while *Cx. quinquefasciatus* is found at low to moderate elevations [49]. Therefore, as global temperatures continue to rise, mosquitoes may also shift to higher altitudes, and thus move into new ecosystems [50].

These shifts occur because of the vectors' direct dependence on suitable climatic conditions for breeding and development. WNV transmitting mosquitoes are ectotherms, which means that their life cycle and phenology is influenced by ambient temperature, modulating their fecundity, development rates, activity (biting rate), and survival. These dependencies can be derived experimentally or from field observations and generally show to be unimodal and species-specific [51, 52]. They explain why episodes of extensive WNV transmission are seasonal in temperate regions where many mosquitoes enter dormancy when winter approaches and why temperatures well above thermal optima reduce the potential for transmission. Additionally, warmer temperatures have been shown to lead to faster replication of the virus within its vector and, thus, to a shorter EIP [53]. Moreover, WNV seems to have higher infection and transmission efficiency at higher temperatures as seen in increases in the vector competence with temperature across a variety of vector species [53–55]–albeit the response of these parameters to temperature is again expected to be unimodal [51, 52].

Furthermore, mosquito vectors rely on water availability to lay eggs and complete their reproduction cycle. Therefore, increased precipitation is believed to elevate vector abundance by increasing the number of potential breeding sites. On the other hand, during drought humans store water which provides artificial water pools preferred by some *Cx.* mosquitoes. Drought conditions can also benefit larval mosquito populations by disrupting food-web structures and leading to higher concentration of nutrients in available water sources [56, 57]. Additionally, some research has suggested that heavy rainfall can lead to flushing of eggs, larvae, and pupae of mosquitoes breeding in drains and ditches [58, 59]. Therefore, there is not a strictly positive or negative association between precipitation and beneficial conditions across all WNV vectors and precipitation regimes. Nevertheless, overall increased precipitation and both a more frequent occurrence of extreme rainfall and droughts, which is expected in climate change scenarios, has significant direct effects on vector population dynamics.

Avian hosts and climate

Several animal species are susceptible to WNV infection [60], however, it is primarily bird species that develop high enough viraemia to infect arthropod vectors and thus sustain the enzootic cycle of WNV via bird-mosquito-bird transmission [61]. Hundreds of bird species have been identified as susceptible to WNV infection and are considered the natural reservoir of the virus [1]. This diversity allows WNV to spread in both sylvatic and synanthropic transmission scenarios, in rural and urban areas wherever susceptible hosts and competent vectors co-occur [62].

Despite this ubiquity, bird species greatly differ in their susceptibility to WNV. While some species develop high viraemia (particularly passerine birds), others are more resistant to infection [61]. In addition, many bird species that act as WNV reservoirs do not present clinical signs of infection, yet certain bird species have shown to frequently develop disease and suffer high mortality rates [63]. In fact, mortality upon wild birds, especially corvids, has been used as an early surveillance signal of WNV activity [64]. Although factors influencing susceptibility to infection and disease are complex and still poorly understood, some that have been studied include age, life history, genetics, immunocompetency and behavioral ecology [25], in addition to the different viral strains that the birds are exposed to [65–67]. As described for other diseases in wildlife, closely related bird species may present similar degrees of susceptibility to WNV [68]. Young birds with less developed immune systems are more likely to develop high viraemia [61], and there is evidence that hatch-year birds are key amplifying hosts due to their lack of prior exposure to the virus and because they might be more prone to mosquito bites [69]. Bird immune systems thus play a central role in the susceptibility of the species and therefore the opportunity of the virus to replicate widely [70]. A first exposure to the virus triggers adaptive immune responses such as the production of neutralising antibodies that can remain present and protective against future WNV infections [71]. This is an important point to consider when evaluating prevalence of infection in bird populations through serosurveillance. There is evidence of WNV humoral response in birds being protective against St. Louis encephalitis virus (tough, interestingly, not the other way around) [72], suggesting some level of cross-protection against other flaviviruses [73].

For identifying host species contributing most to amplification of WNV, host competence is an important concept which describes the ability to acquire, maintain and transmit the virus. Studies in the lab on American species involving virus inoculation concluded that blue jays, common grackles, house finches, American crows, and house sparrows are the most competent out of 25 tested species [63]. Here, a host competence index was calculated from each species' viraemia profile and a generalized viraemia-infectiousness relationship. While this can provide a preliminary indication of the relative host competence of different species (see also [74]), it is important to consider that lab studies may not reflect real-world conditions and are usually restricted to a limited number of species [75]. Moreover, Vaughan et al. [76] recently demonstrated that viraemia-infectiousness relationships can significantly depend on the source of the viremic blood. The authors found American robins to be significantly more infectious than common grackles at similar or even lower levels of viraemia, which highlights the risk of misclassifying host competence based on viraemia profiles alone. Overall knowledge on WNV host competence seems to be far from complete.

Clearly, bird species' relative role in viral amplification is not only determined by their physiological ability to transmit WNV. The abundance of bird species and their attractiveness to mosquitoes are at least as decisive. Studies in North America incorporating *Cx. pipiens*' feeding preference with host competence (as derived from the species' typical viraemia profile) and abundance demonstrated that American robins are the main amplifying host in the considered regions. They were shown to be significantly overused as blood meal source when compared to their relative abundance in the avian community which let them act like super spreaders [30, 38, 77]. Other competent species were found to be less important because they were either significantly avoided by mosquitoes or were relatively rare in the study area. Later studies showed that the relative importance of bird species may vary between regions [64], season, and even on fine-spatial scales influenced by the host community composition [39]. For example, in Atlanta it was observed that *Cx.* mosquitoes significantly bite on moderately to poorly competent species (as suspected by their typical viraemia profiles), like northern cardinals or mimids, especially during peak transmission months and in certain urban microhabitats, where these species may slow down amplification and reduce the risk of spillover to humans [39]. A study from northern Italy combining blood-meal analysis and host abundance indicated that blackbirds and Eurasian magpies (as preferred blood meal sources), as well as house sparrows and collared doves (as abundant species that mosquitoes opportunistically feed upon), may be the main amplifiers in a European avian community [34]. The fact that amplification and spillover potential of WNV seem to depend on avian community composition and certain key species can act as sources or sinks of transmission by attracting a large part of mosquito bites, may explain why associations of avian diversity per se to WNV risk have led to ambiguous results [78–81].

Avian serosurveys may elucidate further factors determining which species are regularly exposed to WNV. Previous studies suggest a positive correlation between seroprevalence and the animals' body size which can be attributed to the birds' longevity, and higher attraction of vectors towards larger hosts [82, 83]. In addition, exposure to the virus seems to be modulated by migratory behavior. While some of the European studies do not support significant differences in seroprevalence between migratory and non-migratory species [83, 84], others found greater seroprevalence in migratory than resident birds, suggesting that the migratory birds spend part of their lives in southern areas with greater circulation of the virus than in the sample areas [82, 85–87]. In contrast, studies from California showed that migratory birds entering this state from southern wintering sites are rarely found antibody positive, more likely acquiring infection after entering the state, and that resident birds tend to be more often seropositive than migratory birds [88, 89]. Similarly, migratory birds sampled along eastern and midwestern flyways in the USA more frequently showed seropositivity when sampled during fall migration compared to spring migration [90].

These observations indicate that host distribution and mobility is an important factor to consider in WNV ecology. The ability of birds to travel long-distances particularly manifests during migration but even resident birds can move significant distances during dispersal episodes. How bird movements relate to the spatial spread of WNV is not understood in depth but currently it is thought that (i) migratory birds play an important role in introducing viral strains to new regions, (ii) dispersing resident birds and short-distance migratory birds contribute to the virus movement locally and are important for establishing and maintaining WNV in a specific region.

Twice a year, driven by seasonality, bird migration rearranges the global distribution of the avian community in response to biological needs. This provides a mechanism through which pathogens can be spread along migration routes harboring the potential to establish new endemic foci at great distance [91]. Migratory birds have long been suspected to play a significant role in dispersing WNV from Africa to Europe. Birds infected on their southern wintering grounds could carry the virus northward during spring migration where it reaches European wetlands and urban areas, potentially initiating virus circulation [92, 93]. In fact, there is evidence that migrating birds may have been responsible for several movements of WNV strains via migratory routes connecting Africa, the Middle East, and Europe [94–98] and the location under migratory routes was shown to be a significant risk predictor for European areas to be affected by human WNF [99]. With the ongoing expansion of WNV in Europe, there is now substantial risk of dispersion not only from southern areas in spring but also from Central and North-Eastern European countries during fall migration [100].

The introduction of WNV to the USA in 1999 gave the opportunity to study how WNV moves in a completely naïve but conducive environment with large populations of susceptible hosts and vectors. In fact, the virus spread from coast to coast within four years. It is now believed that several agents, including infected migratory and dispersing resident birds contributed to this rapid expansion [16, 93, 101]. This is based on phylogenetic studies, correlating the pattern of WNV circulation with migration pathways [102, 103], lab investigations presenting evidence that birds infected with WNV maintain their migratory disposition during the infectious period [104], modeling studies coming to different conclusions either suggesting the movement pattern of WNV is well explained by dispersing resident birds [105] or showing an involvement of rapid, long-distance movements [106, 107], and the already discussed evidence from seroprevalence studies.

The American seroprevalence studies also suggest a limited role of migrating birds in regularly transporting the virus south to north and support the absence of an extensive source of year-round WNV transmission in the Neotropics [108]. Additionally, while there is apparent gene flow between different geographic regions, likely mediated by bird movements [94, 109–111], phylogenetic analyses across the USA and Europe support local persistence, often presenting genetic similarity between strains detected in the same locations across subsequent transmission seasons [96, 109–117]. This suggests that, although WNV shows sporadic long-range movement, seasonal transmission of the virus in temperate regions where cool winter temperatures slow down or interrupt horizontal transmission does not depend on continued reintroduction but is supported by a combination of overwintering mechanisms such as low-level horizontal transmission, vertical transmission in dormant vectors, bird-to-bird transmission, and persistent bird infection [15, 70, 108].

As a result of species-specific evolutionary processes, many biological and life history traits in birds are shaped by the environmental conditions of their habitats. Some species are particularly sensitive to shifts in climatic conditions. In the recent past changes have been observed in species' migration timing, migration routes, distribution, as well as the species richness, abundance, and composition of avian assemblages, likely caused by many factors including climate change [118–123]. For example, increasing spring temperatures have been linked to changes in the proportion of migratory species in European bird communities [124]. Moreover, there is a trend for earlier spring arrival of long-distance migratory birds to temperate regions triggered by complex effects of multiple climate indices at their breeding and non-breeding grounds [125]. A recent study estimated that at least half of the magnitude of long-term changes in egg laying date, body condition, and number of offspring in European birds are driven by warming temperatures [126], demonstrating the impact that global warming is having on natural populations' physiology. Therefore, climate change should be expected to bring significant alterations to avian populations and the migration system, directly or indirectly through ecosystem change, that will have carry over effects on the emergence and distribution of WNV.

Eco-epidemiological models of WNV

To understand how the complex and often nonlinear impacts of climate and environment on the vector-host-pathogen nexus (Fig 1) propagate to the risk of WNV transmission, eco-epidemiological models of WNV spread provide a powerful tool. Broadly speaking, these are divided into two types of methodological approaches that have distinct benefits and limitations. While data-driven models are typically used to associate WNV circulation with certain climatic, ecological, and other relevant conditions [127, 128], process-based models explicitly describe the dynamic interactions between vectors, hosts and the environment that lead to disease transmission [129, 130] (see Box 1 for more details). Process-based models often involve substantial simplifications of reality and require calibration to observed data. On the other hand, data-driven models may incorporate process-based elements, such as using temperature-dependent R_0 as a covariate instead of temperature directly [131]. Therefore, a strict separation of data-driven and process-based approaches is not always possible or desirable.

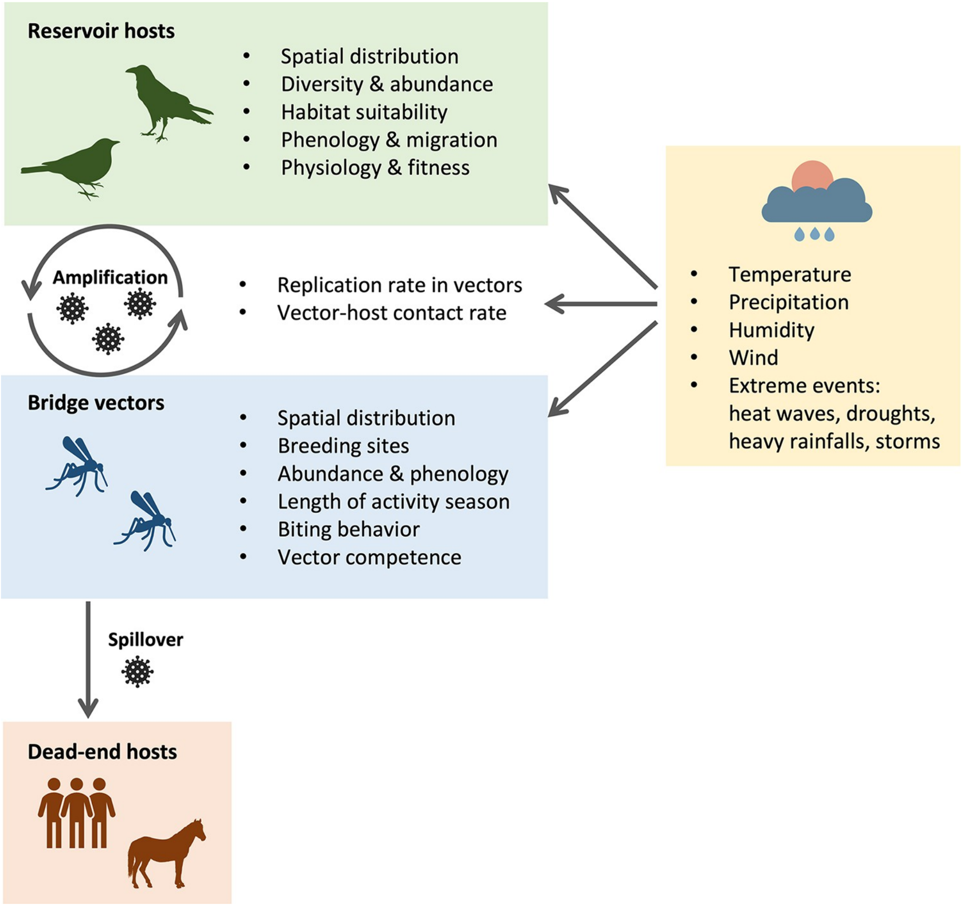

Fig 1. Illustration of the WNV transmission cycle and major known climate sensitive factors affecting transmission through the vector-host-pathogen nexus.

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Box 1. Techniques used in WNV eco-epidemiological risk modeling

Data-driven models use statistical and machine learning techniques to estimate prevailing associations between a set of selected covariates and disease occurrence, aiming to infer the most influential drivers of transmission and/or predict high-risk areas. Data-driven models can beparticularly useful for short-term predictions and early warnings of WNV risk as they can consider a large set of covariates and extrapolate from data collected under present/past conditions, without an imperative need to make hypotheses about the underlying mechanisms. This, however, also limits their ability to predict WNV risk when entering unprecedented data regimes like in climate change scenarios. Insights derived from these models are in most cases of correlative nature generating limited knowledge on causality.

Process-based models aim to capture the biological mechanisms underlying transmission of pathogens in their dynamic equations and provide a tool to simulate transmission dynamics. Deterministic population-level models are often used as an analytically tractable, but highly simplified, method to reveal mechanisms behind general patterns of disease spread. In addition, at this level of complexity it is often possible to derive a representation of the basic reproduction number R0 –the expected number of hosts to be infected by a single infected host in a susceptible population–in terms of parameters of the model. Process-based models can be made increasingly complex, up to stochastic individual-based models, which in principle allow to model arbitrary heterogeneity in the system. If all relevant aspects of transmission are translated to mathematical equations, process-based models are a powerful tool to extrapolate beyond known conditions. In practice their derivation, validation, and parameterization are challenging and require high-quality data.

Improved availability of climatic and environmental data, combined with advancements in affordable computational power, have led to an increasing use of machine learning models (such as tree-based methods, maximum entropy methods, and ensemble approaches) [128, 132–135] and Bayesian spatiotemporal models [127] to predict WNV. These methods tend to trade their flexibility and higher predictive capabilities for lower interpretability. Less complex models, like non-spatial logistic regression [99] or linear mixed effect models [136], can offer a straightforward solution to infer associations between drivers and disease occurrence. In a recent study, Marini et al. [137] presented a highly interpretable approach by modeling the WNV force of infection through normal distributions. They related the peak timing, variance, and overall intensity of predicted cases to covariates, demonstrating that such simple models can offer a reliable approach for infering drivers when eco-epidemiological data is scarce. There is a growing interest in developing explainable artificial intelligence frameworks to improve interpretability in complex models, which have already been used to identify important drivers of WNV risk [128]. Both highly predictive models, for forecasts and risk assessments, and explainable models, for better understanding of drivers and identification of intervention and control targets, play an important role in WNV research.

Process-based models are inherently explainable but the complexity of the WNV transmission cycle and limited availability of data on vector-host ecology and disease occurrence often challenge their usefulness in accurately describing WNV spread. A wide variety of models with different degrees of complexity have been proposed in the literature, ranging from relatively simple dynamical system that offer analytically tractable insights into WNV control strategies [138] to more recently developed models that explicitly account for bird movements [139], mosquito host preference [130], or avian host heterogeneity [78]. In addition, climatic drivers of WNV are increasingly incorporated in process-based models to account for their impact on transmission dynamics [129, 130, 140] or to derive climatically dependent expressions of R_0 or related transmission suitability indices [51, 141, 142]. These approaches mainly consider mosquito-pathogen trait variations due to temperature [51, 129, 140, 142]. Some models also account for the influence of rainfall on the availability of suitable mosquito breeding habitat [143], the effect of humidity on vector biting and mortality [142], or the impact of photoperiod on mosquito diapausing [129, 143].

Climate and land cover drivers of WNV

Several modeling studies have provided valuable insights on the role of climatic conditions and land cover features in shaping the spatial-temporal heterogeneity in WNV risk, which is usually measured by some metric assessing the disease incidence or infection rates in humans, mosquitoes, birds, or equids.

A positive association has been repeatedly found between increased WNV risk and high temperatures [99, 127, 128, 136, 137, 144–150]. Mechanistically it is understood that part of this sensitivity results from the impact of temperature on the vectors and the pathogen described earlier. In a recent study the thermal response of vector-pathogen traits measured at constant temperature for several *Cx*. species and WNV has been incorporated into a process-based relative R_0 model [51]. Evidence from this approach shows a unimodal response of R_0 to temperature with transmission potential peaking between 23˚C and 26˚C with thermal limits and optima for transmission varying between vector species (Fig 2). Although focusing only on specific aspects of WNV transmission, this relative risk measure was shown to be consistent with human case data mapped out by mean summer temperatures in North America further supporting a unimodal (instead of a strictly positive) response of WNV risk to temperature. Similar indices were also shown to be compatible with patterns of WNV circulation in Europe [141, 142].

For precipitation the picture seems less clear. Some studies found a negative correlation between high precipitation and WNV risk [127, 128, 148, 151], while others found a positive correlation [136], indicate that it depends on the region considered [145, 146, 152], or did not find any significant relationship [137]. More direct measures of land surface wetness, that might be more relevant to mosquito dynamics, have also been considered including remotely sensed indices of water availability [99, 128, 136], or measures of soil moisture from hydrological models [131, 153, 154]. It is thought that drought-like conditions can impact transmission dynamics directly by increasing vector-host contact due to aggregation of both around remaining water sources [153], adding to the complex and conflicting mechanisms with which water availability influences vector population dynamics.

A recent Europe-wide study found that a considerable part of the WNV risk may be explained by the preceding year's climate trends, in particular by the mean summer temperature [128]. Other climatic predictors have been identified such as a mild winter [145, 147], low winter precipitation [128] and total annual precipitation from the preceding year, the later one presenting conflicting evidence [151, 152]. The impact of winter conditions might be due to influences on the overwintering success of WNV and the intensity and start of early transmission in temperate regions. In addition, the sequence of conditions leading into the summer appears to be a decisive precursor for the intensity of the transmission season. The study by Farooq et al. [128] indicates that low water availability throughout the first half of the year and high spring temperatures are correlated with WNV outbreaks. The latter is also supported by the findings of Marini et al. [137]. A recent review suggests that the severe WNV outbreak in Europe in 2018 might have been driven by a wet spring that offered suitable conditions for vector populations to expand while the following summer drought could have led to exacerbated transmission [15]. This sequence of events was also observed to be positively correlated with WNF in an analysis of earlier outbreaks in Europe [136] and linked to human WNV cases in eastern Colorado [154]. Similarly–but somewhat flipped–a study looking at WNV transmission to humans and sentinel chickens in Florida found that drought conditions in spring followed by a wet summer are positively correlated with WNV outbreaks [153]. Within the summer months high temperature again shows up as a consistent predictor of transmission [99, 150] and seems to unfold its impact with a time lag of 0–4 weeks [127, 146]. The inclusion of temperature-forcing and precipitation dependence has also shown to improve the outbreak forecast potential of process-based transmission models [140, 143].

Various land cover and geographical features have been linked to WNV transmission. For example, the study by Myer and Johnston [127] concluded that suburban and peri-urban areas where mosquito and bird populations may experience high contact intensity might be at highest risk of infection in mosquitoes. Both a high NDVI (a remotely sensed measure of

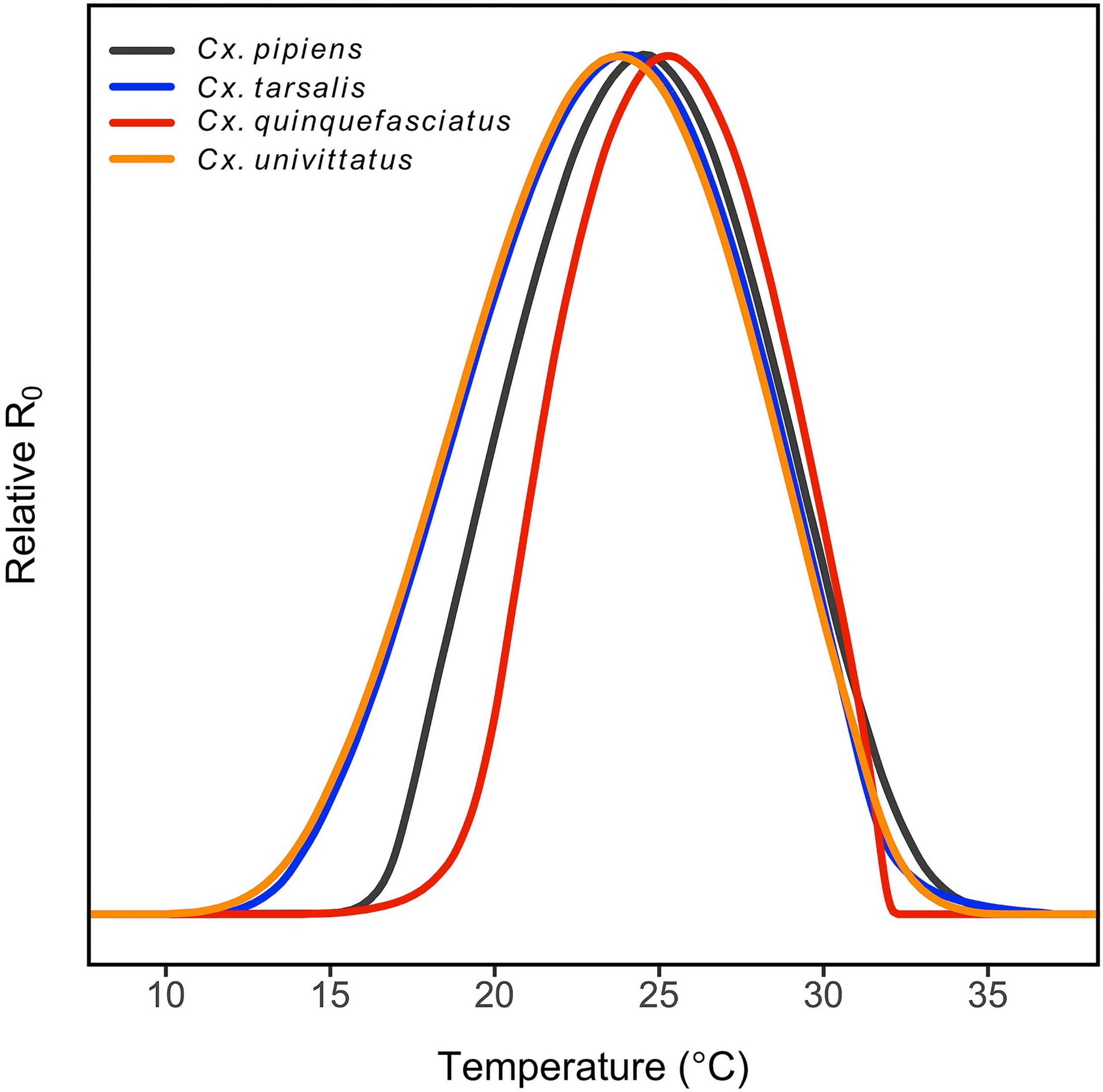

Fig 2. Unimodal thermal response of relative R_0 for WNV in four vector species adapted from [51]**.** WNV in *Cx. pipiens* (dark grey), *Cx. tarsalis* (blue), *Cx. quinquefasciatus* (red), and *Cx. univitattus* (orange).

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greenness), indicating suitable habitat for birds but not necessarily for the considered container-breeding *Cx.* species, and high intensity urban development, frequently inhabited by the mosquitoes but not birds, were shown to be negatively correlated to the incidence of WNV in trapped mosquitoes in Nassau County, New York. Interestingly, a similar work on the neighboring Suffolk County [155] did not find any influence of developed areas on WNV incidence, underlining the importance of deriving these associations for individual areas. Zoonotic transmission has been linked to both rural and urban areas. In the USA, for example, human cases of WNV infection have been positively associated with urban land covers in North-eastern regions but with agricultural land covers in the Western United states, which has been explained by the habitat preferences of the respective dominant WNV vector species, i.e., the *Cx. pipiens* complex in the Northeast and *Cx. tarsalis* in the West [42]. In Europe WNV circulation is predominantly associated with natural and anthropized semi-natural areas [137], although it should be noted that several large human outbreaks have been documented in urban areas [14]. A recent study looking at phylogeographic patterns indicates that areas with high agricultural activities may accelerate and attract the spread of WNV in Europe and that WNV also tends to spread towards areas with a high level of urbanisation and a high coverage of wetland [156]. WNV occurrence in mosquitoes, birds, and equines has been linked to low altitude, presence of wetlands, heterogeneous agricultural areas, and various other land use types in Europe and the Mediterranean [135, 149, 150]. Similarly, various geographical covariates have been associated with the incidence of human WNV cases or outbreaks in Europe, including the presence of wetlands, the location of preceding years' outbreaks [99], the presence of rain-fed agriculture, rivers, and low altitude [144], and the percentage of area covered by irrigated croplands and populated forests [136].

Paz [22, 23] additionally reviewed the potential impact of relative humidity and wind on WNV epidemiology and found only very limited research. Besides effects of humidity on vector population dynamics, correlations to hospital admission dates and morbidity in humans is reported for some regions although air temperature consistently seems to be the better predictor. Wind was reported as a potential mechanism impacting WNV through wind-blown mosquitos and by affecting bird migration via storm tracks. We also want to highlight a recent systematic review giving a detailed overview of studies relating environmental factors to WNV circulation in European and Mediterranean countries [157]. This article also demonstrated that most studies are currently focused on WNV vectors or mammal hosts while studies looking at environmental drivers of WNV in birds or the complete transmission cycle are underrepresented.

Trends in WNV risk and projections under climate change scenarios

Given the established relationships between biotic and abiotic conditions and WNV risk, projecting these factors forward is of invaluable importance to understand which areas will be potential future hotspots of transmission or will be at risk of introduction. Since most of the USA is currently experiencing average summer temperatures (based on 2001–2016 data) below the optimal temperature for transmission indicated by their temperature dependent R_0 model, Shocket et al. [51] expect a net increase in WNV transmission in response to global warming if all other factors would remain constant. Additionally, they anticipate that warming may extend the transmission season and increase risk in higher latitudes and altitudes, while some areas may experience summer temperatures above the thermal optima that may lead to a reduced overall transmission or a bimodal transmission season. The 2022 Lancet countdown Europe report [158] includes a trend prediction from 1951 to 2020 on WNV risk in Europe driven by climate factors. Based on the machine learning model by Farooq et al. [128], an accelerating trend for increased WNV risk is reported with the largest increases in risk in northern and western Europe but with absolute risk remaining highest in southern, central, and eastern Europe. Recently, the authors also applied this model to different combined shared socioeconomic pathways and representative concentration pathways (RCPs), standing for a range of future climate change and socioeconomic scenarios [159]. This analysis indicated that the land areas at WNV risk in Europe could increase from currently (baseline 2000–20) 15%

to 23–30% with an additional population at risk of 161–244 million mid 21st century, depending on the considered scenario, and with most notable increases in Western Europe.

So far, few other studies explicitly projected WNV risk under climate change scenarios. Based on a statistical model that identified drought and immunity as the primary drivers of interannual variation in WNV across the USA, Paull et al. [131] found that projections of drought severity under (RCP) 8.5, which can be seen as a worst-case scenario, could double the annual WNV cases by the mid-twenty-first century. Ewing et al. [129] assessed the risk of WNV introduction to the UK using temperature projections under RCP 8.5. Their process-based model accounts for the temperature-dependent seasonality in vector abundance, the temperature dependence of pathogen development rates and a seasonal-forcing in host birth rates. They also test different timings within the year for WNV introduction by migratory birds. Their findings indicate that the current climate in the UK is insufficient for WNV introduction, but the risk of transient outbreaks might extensively increase in the latter half of the 21st century. Some more projections using data-driven or process-based models have been generated [62, 132, 147, 148, 160, 161] generally showing the potential for an overall increase in transmission intensity and area under climate change but also predicting possible decreases for certain areas.

Further research needs

As of today, there is a consensus that climate change is having multifaceted effects on the transmission of WNV. There is still however a need for more data integration and holistic systems approaches to deepen the understanding further. Predicting WNV risk has proven exceptionally difficult, and while some relationships between drivers and disease occurrence have been established, eco-epidemiological models can, so far, only explain parts of the extreme spatial-temporal variability at which WNV infections occur. Additionally, in most cases, they seem only applicable on limited spatial scales, also narrowing the scope of current WNV climate change projections.

To some degree our limitations to predict and project WNV risk are due to knowledge gaps in the transmission cycle of WNV. There is a need to characterise in more depth the interplay of vector and host distribution, abundance, competence, and vector feeding preferences which has so far been studied only for a few species and study sites. These factors, which vary spatially and seasonally, have shown, however, to be important interrelated determinants of transmission and spillover, and that some species may play key roles in this complex system. Ideally, models would incorporate all components of the transmission cycle including the force of infection between all relevant species pairs in the system while accounting for mosquito biting preferences, species' movement, habitat and phenology, land use and climatic conditions on a fine spatial scale similar to the framework envisioned by Kain et al. [78].

So far, however, many studies are limited by the lack of high-quality granular biological, ecological, and epidemiological observational data. Studies that integrate avian host distribution to estimate WNV risk, for example, often have to extrapolate from limited host competence experimental data [78, 162], are facing sparse distribution data on the considered spatial scale [128] or lack vector population data, thus carrying substantial uncertainty on an integral part of the transmission cycle [78, 83]. Better characterization of avian species' role in the WNV cycle would not only help to map risk, but if certain key species could be identified (like it was the case with the American robin in regions of North America), further studies could investigate species-specific data and examine the influence of their behavior (e.g., their foraging, nesting, roosting, and migration) on transmission dynamics. Such efforts could, for example, shed further light on the role of avian movements as a mechanism influencing local dynamics (by shaping host availability for mosquito bites and dispersing infection locally), and the long-distance spread of WNV strains via migratory birds.

Strengthening data collection and sharing is therefore an important step to understand WNV dynamics in general, and ultimately how it is impacted by climate change. While major investments in data collection and technology have led to a wealth of robust (observed and simulated) climate and meteorological data, the data on biological and ecological processes and disease occurrence is often more resource-exhaustive, tend to be scarce, delayed and often biased [163–165]. However, there are promising developments in data collection, management, and analysis that are likely going to increase the availability of more complete and high-quality data sets in the future. These include, for example, the advent of technological advancements such as remote sensing, mosquito smart traps, and improved animal tracking devices as well as an increasing implementation of citizen science approaches [166–169].

Eco-epidemiological models that integrate improved and novel data streams with climatic and environmental data should not only increase our ability to predict WNV but also our understanding of climate-driven effects on transmission. To achieve this goal, it will be important to build explainable models that complement highly predictive approaches, as this will help to disentagle drivers' individual effects and lead to a better assessment of intervention and control strategies. Though temperature is arguably the best described predictor, effort needs to be invested to quantify and integrate its (long-term) impact on every layer of WNV transmission in more detail beyond vector-pathogen traits, including hosts, habitats, and vector-host interaction. Consideration of other drivers like precipitation and land cover has led to ambiguous results that appear to be very region-specific and scale dependent. With an improved understanding of the transmission cycle and better region-specific data, it could be feasible to link these differences to local vector-host populations, habitat suitability including hydrological conditions, as well as potential human influences including land use and control measures that lead to unique dynamics. Simultaneously to building this fine scale understanding, effort should be put towards identifying more broad scale patterns that make large-scale predictions feasible. For example, it might be valuable to shed more light on which sequences of climatic conditions are precursors for an exacerbated transmission season.

Thus, many climate-driven impacts on WNV have been identified and many more are yet to be better understood and quantified. Projections of WNV risk, though agreeing on an overall trend of increasing risk, are still scarce and highly uncertain. They are limited in spatial scale and often extrapolate from associations derived from past/current conditions [62, 147, 148, 159–161] and/or confine to projecting only one aspect of climate-driven impacts on WNV, e.g., by focusing on temperature and/or vector-pathogen traits [62, 129, 161]. Thus, while these approaches are sophisticated and highly valuable, they could be complemented by projecting indicators that consider more drivers and by integrating process-based relationships in these models wherever feasible. Integrating a deeper mechanistic understanding would increase their ability to extrapolate beyond present-day conditions [170, 171], resulting in more reliable projections.

While improved projections up to the mid-21st century will be important to inform climate risk assessment and adaptation and where investments in surveillance and control systems are needed, long-term projections beyond mid-century are also needed to estimate the role of climate change mitigation and illustrate the impact of high emission high warming scenarios. We could imagine, for example, an approach that combines projections of avian species' distribution integrated with projections for mosquitoes and combined with a spatialized R_0-model that accounts for both host density and distribution to account for host community composition [78] and vector density and distribution to account for species-specific temperature-dependent vector-pathogen traits [51, 172].

To maintain a systems perspective, we further need holistic assessments that consider the impacts of climate change on WNV in context of various other factors that will undergo changes in the future. The predicted increase in urbanization, deforestation, and agriculture would additionally influence directly or indirectly the ecology of WNV as the distribution and abundance of both hosts [173] and vector [31] species is affected. Heightened loss and fragmentation of habitat could lead to bottlenecks exacerbating WNV sharing in wildlife and the fact that human WNV cases already mainly occur in human-modified areas is echoing that encroachments into wild habitats have to be seen as a risk factor for increased zoonotic transmission [174]. Various other relevant determinants of WNV transmission will undergo changes in the future like immunity patterns [131], socio-economic development [175–177], and human behavior, including potential mitigation and adaptation strategies, travel, and trade. In addition, our understanding of the mechanisms driving WNV transmission under climate change is suspect to the uncertainty of possible adaptive (co-)evolution of virus, vectors, and hosts (e.g., it is very well possible that future temperature response curves of mosquito-pathogen traits could show adaptation to new environmental conditions). More frequent and intense outbreaks due to climate change, including faster viral replication at high temperature, would offer more opportunities for viral evolution, potentially accelerating the adaptation of the pathogen to novel conditions as well as benefiting the emergence of high-fitness strains. Moreover, alterations to the avian migration system and species distribution shifts could open new routes of viral sharing between specific geographical areas and species. Models and projections accounting for these processes would further increase our ability to foresee the range of possible future scenarios.

Fostering transdisciplinary thinking

The case of WNV underlines once again that the health of animals, humans, and the environment is deeply intertwined and highlights the urgency to maintain a systemic and global perspective about the health threats emerging at that interface, particularly in the context of climate change.

A collaborative approach is needed to understand all the components of infectious disease dynamics and how these are impacted by ongoing environmental change. This goes beyond modeling studies, from the collection of data under an integrated surveillance system framework, to its analysis, to informing the implementation of policies and interventions, also beyond the health sector. The One Health concept stands out for fostering this kind of joint work highlighting collaborative efforts across multiple disciplines and sectors at local, national, regional, and global levels with the goal of achieving optimal health outcomes for people, animals, and our shared environment [178]. Clearly, addressing the research needs discussed in the previous section will require adopting this transdisciplinary thinking to prevent siloed approaches and increase communication and information sharing between experts from different fields. In this context, knowledge, technology, and financial resources need to be directed towards integrated surveillance and monitoring systems that cover disease surveillance across populations (including humans and other animal hosts). To leverage their full potential for research and monitoring such efforts should be harmonized and standardized across national borders, developing a culture of transnational data sharing [15]. Ultimately, improved and coordinated data collection–including reservoir, vector, host, and environmental information–will allow the development of functional early warning systems which can be implemented in preparedness plans. In some Italian regions, for example, the detection of WNV by their systematically shared entomological surveillance system informs the posterior screening of human blood donations and organs, allowing early case detection and control, as well as more efficient resource allocation [179].

Studying the dynamics of WNV through a One Health lens will enable us to craft policies and interventions aiming at containing risks earlier (e.g., at the animal reservoir source). These studies could help focus surveillance geographically and temporally, allowing for a more targeted resource allocation and informing on the need of control plans to reduce the risk of spillover and spread of outbreaks if it occurs. Additionally, partnerships resulting from collaborations (both in research and policy) not only allow to better understand and address complex phenomena, but also to overcome inefficiencies and work overlap [180]. To achieve this, improving advocacy and communication at government level is vital to promote the interdisciplinary One Health approach beyond the health sector.

It is important to implement a One Health approach considering multifaceted issues and solutions beyond the direct impact of zoonotic pathogens and spillover events at the human-animal interface. Other aspects such as social, economic, and environmental issues must be factored in. For example, the incursion of WNV into domestic bird populations, and what this means for poultry production, food security and the local economies, or the combined impact of land use and climate change on local biodiversity, and how this can ultimately affect ecosystem health and dynamics including ecosystem services on which we depend.

Conclusion

Climate-driven impacts on multi-host, multi-vector viruses like WNV are complex, involving a range of interactions across ecological processes, biological mechanisms, and social determinants. Environmental changes alter the geographical extent and intensity of transmission by affecting vector breeding and pathogen replication. In addition, impacts on host populations and host movement, land use changes and evolutionary processes are bringing changes to the dynamics of WNV that may alter its burden on animal and human health. Appropriate prevention and control will rely on our ability to understand the WNV transmission cycle, its dependence on environmental conditions and to improve our ability to predict and project WNV risk. In this knowledge generation eco-epidemiological models play an important role by providing quantitative evidence for attribution, and potential future scenarios which can guide monitoring and resource allocation. A bottleneck in carrying out this research, however, is the lack of true interdisciplinary and trans-sectoral approaches. Understanding and containing infectious diseases, especially those at the interface of human, animal and environmental health requires adopting a One Health approach in data collection, modeling and policy that involves coordination, collaboration, and communication between experts and stakeholders in several fields and sectors at local, national, regional, and global levels. Recognizing that the health of humans, animals and ecosystems are inextricably linked provides a conceptual framework to develop solutions to today's most pressing health and environmental challenges.

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References

1. Petersen LR, Brault AC, Nasci RS. West Nile Virus: Review of the Literature. JAMA. 2013; 310: 308. https://doi.org/10.1001/jama.2013.8042 PMID: 23860989
2. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile Virus: An Update on Pathobiology, Epidemiology, Diagnostics, Control and "One Health" Implications. Pathogens. 2020; 9: 589. https://doi.org/10.3390/pathogens9070589 PMID: 32707644
3. LaDeau SL, Kilpatrick AM, Marra PP. West Nile virus emergence and large-scale declines of North American bird populations. Nature. 2007; 447: 710–713. https://doi.org/10.1038/nature05829 PMID: 17507930
4. Paré J, Moore A. West Nile virus in horses—What do you need to know to diagnose the disease? Can Vet J Rev Veterinaire Can. 2018; 59: 1119–1120.
5. Angenvoort J, Brault AC, Bowen RA, Groschup MH. West Nile viral infection of equids. Vet Microbiol. 2013; 167: 168–180. https://doi.org/10.1016/j.vetmic.2013.08.013 PMID: 24035480
6. Tsioris K, Gupta NT, Ogunniyi AO, Zimnisky RM, Qian F, Yao Y, et al. Neutralizing antibodies against West Nile virus identified directly from human B cells by single-cell analysis and next generation sequencing. Integr Biol. 2015; 7: 1587–1597. https://doi.org/10.1039/C5IB00169B PMID: 26481611
7. Castillo-Olivares J, Mansfield KL, Phipps LP, Johnson N, Tearle J, Fooks AR. Antibody Response in Horses Following Experimental Infection with West Nile Virus Lineages 1 and 2: Antibody Response in Horses with WNV. Transbound Emerg Dis. 2011; 58: 206–212. https://doi.org/10.1111/j.1865-1682.2010.01197.x PMID: 21223533
8. Khatibzadeh SM, Gold CB, Keggan AE, Perkins GA, Glaser AL, Dubovi EJ, et al. West Nile virus–specific immunoglobulin isotype responses in vaccinated and infected horses. Am J Vet Res. 2015; 76: 92–100. https://doi.org/10.2460/ajvr.76.1.92 PMID: 25535666
9. Saiz J-C. Animal and Human Vaccines against West Nile Virus. Pathogens. 2020; 9: 1073. https://doi.org/10.3390/pathogens9121073 PMID: 33371384
10. Ulbert S. West Nile virus vaccines–current situation and future directions. Hum Vaccines Immunother. 2019; 15: 2337–2342. https://doi.org/10.1080/21645515.2019.1621149 PMID: 31116691
11. Smithburn KC, Hughes TP, Burke AW, Paul JH. A Neurotropic Virus Isolated from the Blood of a Native of Uganda 1. Am J Trop Med Hyg. 1940; s1-20: 471–492. https://doi.org/10.4269/ajtmh.1940.s1-20.471
12. Gray T, Webb CE. A review of the epidemiological and clinical aspects of West Nile virus. Int J Gen Med. 2014; 193. https://doi.org/10.2147/IJGM.S59902 PMID: 24748813
13. Sejvar JJ. West nile virus: an historical overview. Ochsner J. 2003; 5: 6–10. PMID: 21765761
14. Paz S, Semenza J. Environmental Drivers of West Nile Fever Epidemiology in Europe and Western Asia—A Review. Int J Environ Res Public Health. 2013; 10: 3543–3562. https://doi.org/10.3390/ijerph10083543 PMID: 23939389
15. Camp JV, Nowotny N. The knowns and unknowns of West Nile virus in Europe: what did we learn from the 2018 outbreak? Expert Rev Anti Infect Ther. 2020; 18: 145–154. https://doi.org/10.1080/14787210.2020.1713751 PMID: 31914833
16. Kramer LD, Ciota AT, Kilpatrick AM. Introduction, Spread, and Establishment of West Nile Virus in the Americas. Reisen W, editor. J Med Entomol. 2019; 56: 1448–1455. https://doi.org/10.1093/jme/tjz151 PMID: 31549719
17. Ronca SE, Ruff JC, Murray KO. A 20-year historical review of West Nile virus since its initial emergence in North America: Has West Nile virus become a neglected tropical disease? Vasconcelos PFC, editor. PLoS Negl Trop Dis. 2021; 15: e0009190. https://doi.org/10.1371/journal.pntd.0009190 PMID: 33956816
18. Yango AF, Fischbach BV, Levy M, Chandrakantan A, Tan V, Spak C, et al. West Nile Virus Infection in Kidney and Pancreas Transplant Recipients in the Dallas-Fort Worth Metroplex During the 2012 Texas Epidemic. Transplantation. 2014; 97: 953–957. https://doi.org/10.1097/01.TP.0000438621.81686.ab PMID: 24827765
19. Centers for Disease Control and Prevention (CDC). Intrauterine West Nile Virus Infection—New York, 2002. MMWR Morb Mortal Wkly Rep 2002; 51:1135–1136. PMID: 12537289
20. Pradier S, Lecollinet S, Leblond A. West Nile virus epidemiology and factors triggering change in its distribution in Europe. Rev Sci Tech OIE. 2012; 31: 829–844. https://doi.org/10.20506/rst.31.3.2167 PMID: 23520737
21. Romanello M, Di Napoli C, Drummond P, Green C, Kennard H, Lampard P, et al. The 2022 report of the Lancet Countdown on health and climate change: health at the mercy of fossil fuels. The Lancet. 2022; 400: 1619–1654. https://doi.org/10.1016/S0140-6736(22)01540-9 PMID: 36306815

22. Paz S. Climate change impacts on West Nile virus transmission in a global context. Philos Trans R Soc B Biol Sci. 2015; 370: 20130561. https://doi.org/10.1098/rstb.2013.0561 PMID: 25688020

23. Paz S. Effects of climate change on vector-borne diseases: an updated focus on West Nile virus in humans. Osborn D, editor. Emerg Top Life Sci. 2019; 3: 143–152. https://doi.org/10.1042/ETLS20180124 PMID: 33523144

24. Colpitts TM, Conway MJ, Montgomery RR, Fikrig E. West Nile Virus: Biology, Transmission, and Human Infection. Clin Microbiol Rev. 2012; 25: 635–648. https://doi.org/10.1128/CMR.00045-12 PMID: 23034323

25. Marra PP, Griffing S, Caffrey C, Kilpatrick AM, McLEAN R, Brand C, et al. West Nile Virus and Wildlife. BioScience. 2004; 54: 393. https://doi.org/10.1641/0006-3568(2004)054[0393:WNVAW]2.0.CO;2

26. Vogels CB, Göertz GP, Pijlman GP, Koenraadt CJ. Vector competence of European mosquitoes for West Nile virus. Emerg Microbes Infect. 2017; 6: 1–13. https://doi.org/10.1038/emi.2017.82 PMID: 29116220

27. Bernard KA, Kramer LD, Ebel GD, Carricaburu J, Young D. GENETIC AND PHENOTYPIC VARIATION OF WEST NILE VIRUS IN NEW YORK, 2000–2003. Am J Trop Med Hyg. 2004; 71: 493–500. https://doi.org/10.4269/ajtmh.2004.71.493 PMID: 15516648

28. Duggal NK, Bosco-Lauth A, Bowen RA, Wheeler SS, Reisen WK, Felix TA, et al. Evidence for Co-evolution of West Nile Virus and House Sparrows in North America. Tesh RB, editor. PLoS Negl Trop Dis. 2014; 8: e3262. https://doi.org/10.1371/journal.pntd.0003262 PMID: 25357248

29. Meola MA, Moudy RM, Morin L-LL, Ebel GD, Kramer LD. A Newly Emergent Genotype of West Nile Virus Is Transmitted Earlier and More Efficiently by Culex Mosquitoes. Am J Trop Med Hyg. 2007; 77: 365–370. https://doi.org/10.4269/ajtmh.2007.77.365 PMID: 17690414

30. Goldberg TL, Ruiz MO, Hamer GL, Brawn JD, Kitron UD, Hayes DB, et al. Host Selection by Culex pipiens Mosquitoes and West Nile Virus Amplification. Am J Trop Med Hyg. 2009; 80: 268–278. https://doi.org/10.4269/ajtmh.2009.80.268 PMID: 19190226

31. Farajollahi A, Fonseca DM, Kramer LD, Marm Kilpatrick A. "Bird biting" mosquitoes and human disease: A review of the role of Culex pipiens complex mosquitoes in epidemiology. Infect Genet Evol. 2011; 11: 1577–1585. https://doi.org/10.1016/j.meegid.2011.08.013 PMID: 21875691

32. Kilpatrick AM. Globalization, Land Use, and the Invasion of West Nile Virus. Science. 2011; 334: 323–327. https://doi.org/10.1126/science.1201010 PMID: 22021850

33. Kilpatrick AM, Kramer LD, Campbell SR, Alleyne EO, Dobson AP, Daszak P. West Nile Virus Risk Assessment and the Bridge Vector Paradigm. Emerg Infect Dis. 2005; 11: 425–429. https://doi.org/10.3201/eid1103.040364 PMID: 15757558

34. Rizzoli A, Bolzoni L, Chadwick EA, Capelli G, Montarsi F, Grisenti M, et al. Understanding West Nile virus ecology in Europe: Culex pipiens host feeding preference in a hotspot of virus emergence. Parasit Vectors. 2015; 8: 213. https://doi.org/10.1186/s13071-015-0831-4 PMID: 25888754

35. Yan J, Gangoso L, Ruiz S, Soriguer R, Figuerola J, Martínez-de la Puente J. Understanding host utilization by mosquitoes: determinants, challenges and future directions. Biol Rev. 2021; 96: 1367–1385. https://doi.org/10.1111/brv.12706 PMID: 33686781

36. Muñoz J, Ruiz S, Soriguer R, Alcaide M, Viana DS, Roiz D, et al. Feeding Patterns of Potential West Nile Virus Vectors in South-West Spain. Schneider BS, editor. PLoS ONE. 2012; 7: e39549. https://doi.org/10.1371/journal.pone.0039549 PMID: 22745781

37. Tiron GV, Stancu IG, Dinu S, Prioteasa FL, Fălcuță E, Ceianu CS, et al. Characterization and Host-Feeding Patterns of *Culex pipiens* s.l. Taxa in a West Nile Virus-Endemic Area in Southeastern Romania. Vector-Borne Zoonotic Dis. 2021; 21: 713–719. https://doi.org/10.1089/vbz.2020.2739 PMID: 34160283

38. Kilpatrick AM, Kramer LD, Jones MJ, Marra PP, Daszak P. West Nile Virus Epidemics in North America Are Driven by Shifts in Mosquito Feeding Behavior. Ostfeld R, editor. PLoS Biol. 2006; 4: e82. https://doi.org/10.1371/journal.pbio.0040082 PMID: 16494532

39. Hedeen DL, Bisanzio D, McMillan JR, Brosi BJ, Mead DG, Hamer GL, et al. Supersuppression: Reservoir Competency and Timing of Mosquito Host Shifts Combine to Reduce Spillover of West Nile Virus. Am J Trop Med Hyg. 2016; 95: 1174–1184. https://doi.org/10.4269/ajtmh.15-0809 PMID: 27503511

40. Fritz ML, Walker ED, Miller JR, Severson DW, Dworkin I. Divergent host preferences of above- and below-ground *Culex pipiens* mosquitoes and their hybrid offspring. Med Vet Entomol. 2015; 29: 115–123. https://doi.org/10.1111/mve.12096 PMID: 25600086

41. Ferraguti M, Martínez-de la Puente J, Roiz D, Ruiz S, Soriguer R, Figuerola J. Effects of landscape anthropization on mosquito community composition and abundance. Sci Rep. 2016; 6: 29002. https://doi.org/10.1038/srep29002 PMID: 27373794

42. Bowden SE, Magori K, Drake JM. Regional Differences in the Association Between Land Cover and West Nile Virus Disease Incidence in Humans in the United States. Am J Trop Med Hyg. 2011; 84: 234–238. https://doi.org/10.4269/ajtmh.2011.10-0134 PMID: 21292890

43. Haba Y, McBride L. Origin and status of Culex pipiens mosquito ecotypes. Curr Biol. 2022; 32: R237–R246. https://doi.org/10.1016/j.cub.2022.01.062 PMID: 35290776

44. Ciota AT, Chin PA, Kramer LD. The effect of hybridization of Culex pipiens complex mosquitoes on transmission of West Nile virus. Parasit Vectors. 2013; 6: 305. https://doi.org/10.1186/1756-3305-6-305 PMID: 24499581

45. Brown HE, Young A, Lega J, Andreadis TG, Schurich J, Comrie A. Projection of Climate Change Influences on U.S. West Nile Virus Vectors. Earth Interact. 2015; 19: 1–18. https://doi.org/10.1175/EI-D-15-0008.1 PMID: 27057131

46. Morin CW, Comrie AC. Regional and seasonal response of a West Nile virus vector to climate change. Proc Natl Acad Sci. 2013; 110: 15620–15625. https://doi.org/10.1073/pnas.1307135110 PMID: 24019459

47. Hongoh V, Berrang-Ford L, Scott ME, Lindsay LR. Expanding geographical distribution of the mosquito, Culex pipiens, in Canada under climate change. Appl Geogr. 2012; 33: 53–62. https://doi.org/10.1016/j.apgeog.2011.05.015

48. Samy AM, Elaagip AH, Kenawy MA, Ayres CFJ, Peterson AT, Soliman DE. Climate Change Influences on the Global Potential Distribution of the Mosquito Culex quinquefasciatus, Vector of West Nile Virus and Lymphatic Filariasis. LaDeau SL, editor. PLOS ONE. 2016; 11: e0163863. https://doi.org/10.1371/journal.pone.0163863 PMID: 27695107

49. Harbach RE. Culex pipiens: Species Versus Species Complex–Taxonomic History and Perspective. J Am Mosq Control Assoc. 2012; 28: 10–23. https://doi.org/10.2987/8756-971X-28.4.10 PMID: 23401941

50. Carlson CJ, Bannon E, Mendenhall E, Newfield T, Bansal S. Rapid range shifts in African *Anopheles* mosquitoes over the last century. Biol Lett. 2023; 19: 20220365. https://doi.org/10.1098/rsbl.2022.0365 PMID: 36789530

51. Shocket MS, Verwillow AB, Numazu MG, Slamani H, Cohen JM, El Moustaid F, et al. Transmission of West Nile and five other temperate mosquito-borne viruses peaks at temperatures between 23˚C and 26˚C. eLife. 2020; 9: e58511. https://doi.org/10.7554/eLife.58511 PMID: 32930091

52. Mordecai EA, Caldwell JM, Grossman MK, Lippi CA, Johnson LR, Neira M, et al. Thermal biology of mosquito-borne disease. Byers J (Jeb), editor. Ecol Lett. 2019; 22: 1690–1708. https://doi.org/10.1111/ele.13335 PMID: 31286630

53. Dohm DJ, O'Guinn ML, Turell MJ. Effect of Environmental Temperature on the Ability of *Culex pipiens* (Diptera: Culicidae) to Transmit West Nile Virus. J Med Entomol. 2002; 39: 221–225. https://doi.org/10.1603/0022-2585-39.1.221 PMID: 11931261

54. Kilpatrick AM, Meola MA, Moudy RM, Kramer LD. Temperature, Viral Genetics, and the Transmission of West Nile Virus by Culex pipiens Mosquitoes. Buchmeier MJ, editor. PLoS Pathog. 2008; 4: e1000092. https://doi.org/10.1371/journal.ppat.1000092 PMID: 18584026

55. Vogels CBF, Fros JJ, Göertz GP, Pijlman GP, Koenraadt CJM. Vector competence of northern European Culex pipiens biotypes and hybrids for West Nile virus is differentially affected by temperature. Parasit Vectors. 2016; 9: 393. https://doi.org/10.1186/s13071-016-1677-0 PMID: 27388451

56. Chase JM, Knight TM. Drought-induced mosquito outbreaks in wetlands: Drought-induced mosquito outbreaks in wetlands. Ecol Lett. 2003; 6: 1017–1024. https://doi.org/10.1046/j.1461-0248.2003.00533.x

57. Cotar AI, Falcuta E, Prioteasa LF, Dinu S, Ceianu CS, Paz S. Transmission Dynamics of the West Nile Virus in Mosquito Vector Populations under the Influence of Weather Factors in the Danube Delta, Romania. EcoHealth. 2016; 13: 796–807. https://doi.org/10.1007/s10393-016-1176-y PMID: 27709311

58. Koenraadt CJM, Harrington LC. Flushing Effect of Rain on Container-Inhabiting Mosquitoes Aedes aegypti and *Culex pipiens* (Diptera: Culicidae). J Med Entomol. 2008; 45: 28–35. https://doi.org/10.1603/0022-2585(2008)45[28:FEOROC]2.0.CO;2

59. Gardner AM, Hamer GL, Hines AM, Newman CM, Walker ED, Ruiz MO. Weather Variability Affects Abundance of Larval *Culex* (Diptera: Culicidae) in Storm Water Catch Basins in Suburban Chicago. J Med Entomol. 2012; 49: 270–276. https://doi.org/10.1603/ME11073 PMID: 22493843

60. Root JJ, Bosco-Lauth AM. West Nile Virus Associations in Wild Mammals: An Update. Viruses. 2019; 11: 459. https://doi.org/10.3390/v11050459 PMID: 31117189

61. van der Meulen KM, Pensaert MB, Nauwynck HJ. West Nile virus in the vertebrate world. Arch Virol. 2005; 150: 637–657. https://doi.org/10.1007/s00705-004-0463-z PMID: 15662484

62. Semenza JC, Tran A, Espinosa L, Sudre B, Domanovic D, Paz S. Climate change projections of West Nile virus infections in Europe: implications for blood safety practices. Environ Health. 2016; 15: S28. https://doi.org/10.1186/s12940-016-0105-4 PMID: 26961903

63. Komar N, Langevin S, Hinten S, Nemeth N, Edwards E, Hettler D, et al. Experimental Infection of North American Birds with the New York 1999 Strain of West Nile Virus. Emerg Infect Dis. 2003; 9: 311–322. https://doi.org/10.3201/eid0903.020628 PMID: 12643825

64. Taieb L, Ludwig A, Ogden NH, Lindsay RL, Iranpour M, Gagnon CA, et al. Bird Species Involved in West Nile Virus Epidemiological Cycle in Southern Québec. Int J Environ Res Public Health. 2020; 17: 4517. https://doi.org/10.3390/ijerph17124517 PMID: 32585999

65. Lim SM, Brault AC, van Amerongen G, Bosco-Lauth AM, Romo H, Sewbalaksing VD, et al. Susceptibility of Carrion Crows to Experimental Infection with Lineage 1 and 2 West Nile Viruses. Emerg Infect Dis. 2015; 21: 1357–1365. https://doi.org/10.3201/2108.140714 PMID: 26197093

66. Del Amo J, Llorente F, Figuerola J, Soriguer RC, Moreno AM, Cordioli P, et al. Experimental infection of house sparrows (Passer domesticus) with West Nile virus isolates of Euro-Mediterranean and North American origins. Vet Res. 2014; 45: 33. https://doi.org/10.1186/1297-9716-45-33 PMID: 24641615

67. Jiménez de Oya N, Camacho M-C, Blázquez A-B, Lima-Barbero J-F, Saiz J-C, Höfle U, et al. High susceptibility of magpie (Pica pica) to experimental infection with lineage 1 and 2 West Nile virus. Brault AC, editor. PLoS Negl Trop Dis. 2018; 12: e0006394. https://doi.org/10.1371/journal.pntd.0006394 PMID: 29634743

68. Longdon B, Hadfield JD, Webster CL, Obbard DJ, Jiggins FM. Host Phylogeny Determines Viral Persistence and Replication in Novel Hosts. Schneider DS, editor. PLoS Pathog. 2011; 7: e1002260. https://doi.org/10.1371/journal.ppat.1002260 PMID: 21966271

69. Hamer GL, Walker ED, Brawn JD, Loss SR, Ruiz MO, Goldberg TL, et al. Rapid Amplification of West Nile Virus: The Role of Hatch-Year Birds. Vector-Borne Zoonotic Dis. 2008; 8: 57–68. https://doi.org/10.1089/vbz.2007.0123 PMID: 18237262

70. Duggal NK, Langwig KE, Ebel GD, Brault AC. On the Fly: Interactions Between Birds, Mosquitoes, and Environment That Have Molded West Nile Virus Genomic Structure Over Two Decades. Reisen W, editor. J Med Entomol. 2019; 56: 1467–1474. https://doi.org/10.1093/jme/tjz112 PMID: 31549720

71. Nemeth NM, Oesterle PT, Bowen RA. Humoral immunity to West Nile virus is long-lasting and protective in the house sparrow (Passer domesticus). Am J Trop Med Hyg. 2009; 80: 864–869. PMID: 19407139

72. Reisen WK, Fang Y. PREVIOUS INFECTION WITH WEST NILE OR ST. LOUIS ENCEPHALITIS VIRUSES PROVIDES CROSS PROTECTION DURING REINFECTION IN HOUSE FINCHES. Am J Trop Med Hyg. 2006; 75: 480–485. https://doi.org/10.4269/ajtmh.2006.75.480 PMID: 16968925

73. Ahlers LRH, Goodman AG. The Immune Responses of the Animal Hosts of West Nile Virus: A Comparison of Insects, Birds, and Mammals. Front Cell Infect Microbiol. 2018; 8: 96. https://doi.org/10.3389/fcimb.2018.00096 PMID: 29666784

74. Kilpatrick AM, LaDeau SL, Marra PP. Ecology of West Nile Virus Transmission and its Impact on Birds in the Western Hemisphere. The Auk. 2007; 124: 1121–1136. https://doi.org/10.1093/auk/124.4.1121

75. Pérez-Ramírez E, Llorente F, Jiménez-Clavero M. Experimental Infections of Wild Birds with West Nile Virus. Viruses. 2014; 6: 752–781. https://doi.org/10.3390/v6020752 PMID: 24531334

76. Vaughan JA, Newman RA, Turell MJ. Bird species define the relationship between West Nile viremia and infectiousness to Culex pipiens mosquitoes. Gubler DJ, editor. PLoS Negl Trop Dis. 2022; 16: e0010835. https://doi.org/10.1371/journal.pntd.0010835 PMID: 36201566

77. Marm Kilpatrick A, Daszak P, Jones MJ, Marra PP, Kramer LD. Host heterogeneity dominates West Nile virus transmission. Proc R Soc B Biol Sci. 2006; 273: 2327–2333. https://doi.org/10.1098/rspb.2006.3575 PMID: 16928635

78. Kain MP, Bolker BM. Predicting West Nile virus transmission in North American bird communities using phylogenetic mixed effects models and eBird citizen science data. Parasit Vectors. 2019; 12: 395. https://doi.org/10.1186/s13071-019-3656-8 PMID: 31395085

79. Levine RS, Hedeen DL, Hedeen MW, Hamer GL, Mead DG, Kitron UD. Avian species diversity and transmission of West Nile virus in Atlanta, Georgia. Parasit Vectors. 2017; 10: 62. https://doi.org/10.1186/s13071-017-1999-6 PMID: 28159002

80. Loss SR, Hamer GL, Walker ED, Ruiz MO, Goldberg TL, Kitron UD, et al. Avian host community structure and prevalence of West Nile virus in Chicago, Illinois. Oecologia. 2009; 159: 415–424. https://doi.org/10.1007/s00442-008-1224-6 PMID: 19034529

81. Swaddle JP, Calos SE. Increased Avian Diversity Is Associated with Lower Incidence of Human West Nile Infection: Observation of the Dilution Effect. Buckling A, editor. PLoS ONE. 2008; 3: e2488. https://doi.org/10.1371/journal.pone.0002488 PMID: 18575599

82. Figuerola J, Jiménez-Clavero MA, López G, Rubio C, Soriguer R, Gómez-Tejedor C, et al. Size matters: West Nile Virus neutralizing antibodies in resident and migratory birds in Spain. Vet Microbiol. 2008; 132: 39–46. https://doi.org/10.1016/j.vetmic.2008.04.023 PMID: 18514437

83. Durand B, Tran A, Balança G, Chevalier V. Geographic variations of the bird-borne structural risk of West Nile virus circulation in Europe. Ciccozzi M, editor. PLOS ONE. 2017; 12: e0185962. https://doi.org/10.1371/journal.pone.0185962 PMID: 29023472

84. Lelli R, Calistri P, Bruno R, Monaco F, Savini G, Di Sabatino D, et al. West Nile Transmission in Resident Birds in Italy: West Nile Transmission in Resident Birds. Transbound Emerg Dis. 2012; 59: 421–428. https://doi.org/10.1111/j.1865-1682.2011.01287.x PMID: 22212727

85. Michel F, Fischer D, Eiden M, Fast C, Reuschel M, Müller K, et al. West Nile Virus and Usutu Virus Monitoring of Wild Birds in Germany. Int J Environ Res Public Health. 2018; 15: 171. https://doi.org/10.3390/ijerph15010171 PMID: 29361762

86. Jourdain E, Zeller HG, Sabatier P, Murri S, Kayser Y, Greenland T, et al. Prevalence of West Nile Virus Neutralizing Antibodies in Wild Birds from the Camargue Area, Southern France. J Wildl Dis. 2008; 44: 766–771. https://doi.org/10.7589/0090-3558-44.3.766 PMID: 18689669

87. López G, Jiménez-Clavero MÁ, Tejedor CG, Soriguer R, Figuerola J. Prevalence of West Nile Virus Neutralizing Antibodies in Spain Is Related to the Behavior of Migratory Birds. Vector-Borne Zoonotic Dis. 2008; 8: 615–622. https://doi.org/10.1089/vbz.2007.0200 PMID: 18399777

88. Reisen WK, Garcia S, Wheeler SS, Fang Y. Migratory Birds and the Dispersal of Arboviruses in California. Am J Trop Med Hyg. 2010; 83: 808–815. https://doi.org/10.4269/ajtmh.2010.10-0200 PMID: 20889869

89. Reisen WK, Wheeler SS. Surveys for Antibodies Against Mosquitoborne Encephalitis Viruses in California Birds, 1996–2013. Vector-Borne Zoonotic Dis. 2016; 16: 264–282. https://doi.org/10.1089/vbz.2015.1888 PMID: 26974395

90. Guptill SC, McLean RG, Dusek RJ, Ebel GD, Ubico SR, Kramer LD, et al. Prevalence of West Nile Virus in Migratory Birds during Spring and Fall Migration. Am J Trop Med Hyg. 2009; 81: 1151–1158. https://doi.org/10.4269/ajtmh.2009.09-0106 PMID: 19996451

91. Reed KD, Meece JK, Henkel JS, Shukla SK. Birds, Migration and Emerging Zoonoses: West Nile Virus, Lyme Disease, Influenza A and Enteropathogens. Clin Med Res. 2003; 1: 5–12. https://doi.org/10.3121/cmr.1.1.5 PMID: 15931279

92. Rappole J. Migratory Birds and Spread of West Nile Virus in the Western Hemisphere. Emerg Infect Dis. 2000; 6: 319–328. https://doi.org/10.3201/eid0604.000401 PMID: 10905964

93. Rappole JH, Hubálek Z. Migratory birds and West Nile virus: MIGRATORY BIRDS AND WEST NILE VIRUS. J Appl Microbiol. 2003; 94: 47–58. https://doi.org/10.1046/j.1365-2672.94.s1.6.x PMID: 12675936

94. May FJ, Davis CT, Tesh RB, Barrett ADT. Phylogeography of West Nile Virus: from the Cradle of Evolution in Africa to Eurasia, Australia, and the Americas. J Virol. 2011; 85: 2964–2974. https://doi.org/10.1128/JVI.01963-10 PMID: 21159871

95. Ciccozzi M, Peletto S, Cella E, Giovanetti M, Lai A, Gabanelli E, et al. Epidemiological history and phylogeography of West Nile virus lineage 2. Infect Genet Evol. 2013; 17: 46–50. https://doi.org/10.1016/j.meegid.2013.03.034 PMID: 23542457

96. Zehender G, Ebranati E, Bernini F, Presti AL, Rezza G, Delogu M, et al. Phylogeography and epidemiological history of West Nile virus genotype 1a in Europe and the Mediterranean basin. Infect Genet Evol. 2011; 11: 646–653. https://doi.org/10.1016/j.meegid.2011.02.003 PMID: 21320643

97. Malkinson M. Introduction of West Nile virus in the Middle East by Migrating White Storks. Emerg Infect Dis. 2002; 8: 392–397. https://doi.org/10.3201/eid0804.010217 PMID: 11971773

98. Hernández-Triana LM, Jeffries CL, Mansfield KL, Carnell G, Fooks AR, Johnson N. Emergence of West Nile Virus Lineage 2 in Europe: A Review on the Introduction and Spread of a Mosquito-Borne Disease. Front Public Health. 2014; 2. https://doi.org/10.3389/fpubh.2014.00271 PMID: 25538937

99. Tran A, Sudre B, Paz S, Rossi M, Desbrosse A, Chevalier V, et al. Environmental predictors of West Nile fever risk in Europe. Int J Health Geogr. 2014; 13: 26. https://doi.org/10.1186/1476-072X-13-26 PMID: 24986363

100. Mancuso E, Cecere JG, Iapaolo F, Di Gennaro A, Sacchi M, Savini G, et al. West Nile and Usutu Virus Introduction via Migratory Birds: A Retrospective Analysis in Italy. Viruses. 2022; 14: 416. https://doi.org/10.3390/v14020416 PMID: 35216009

101. Hadfield J, Brito AF, Swetnam DM, Vogels CBF, Tokarz RE, Andersen KG, et al. Twenty years of West Nile virus spread and evolution in the Americas visualized by Nextstrain. Hobman TC, editor. PLOS Pathog. 2019; 15: e1008042. https://doi.org/10.1371/journal.ppat.1008042 PMID: 31671157

102. Swetnam D, Widen SG, Wood TG, Reyna M, Wilkerson L, Debboun M, et al. Terrestrial Bird Migration and West Nile Virus Circulation, United States. Emerg Infect Dis. 2018; 24: 2184–2194. https://doi.org/10.3201/eid2412.180382 PMID: 30457531

103. Di Giallonardo F, Geoghegan JL, Docherty DE, McLean RG, Zody MC, Qu J, et al. Fluid Spatial Dynamics of West Nile Virus in the United States: Rapid Spread in a Permissive Host Environment. Lyles DS, editor. J Virol. 2016; 90: 862–872. https://doi.org/10.1128/JVI.02305-15 PMID: 26512086

104. Owen J, Moore F, Panella N, Edwards E, Bru R, Hughes M, et al. Migrating Birds as Dispersal Vehicles for West Nile Virus. EcoHealth. 2006; 3: 79–85. https://doi.org/10.1007/s10393-006-0025-9

105. Rappole JH, Compton BW, Leimgruber P, Robertson J, King DI, Renner SC. Modeling Movement of West Nile Virus in the Western Hemisphere. Vector-Borne Zoonotic Dis. 2006; 6: 128–139. https://doi.org/10.1089/vbz.2006.6.128 PMID: 16796510

106. Pybus OG, Suchard MA, Lemey P, Bernardin FJ, Rambaut A, Crawford FW, et al. Unifying the spatial epidemiology and molecular evolution of emerging epidemics. Proc Natl Acad Sci. 2012; 109: 15066–15071. https://doi.org/10.1073/pnas.1206598109 PMID: 22927414

107. Peterson AT, Vieglais DA, Andreasen JK. Migratory Birds Modeled as Critical Transport Agents for West Nile Virus in North America. Vector-Borne Zoonotic Dis. 2003; 3: 27–37. https://doi.org/10.1089/153036603765627433 PMID: 12804378

108. Reisen WK, Wheeler SS. Overwintering of West Nile Virus in the United States. Andreadis T, editor. J Med Entomol. 2019; 56: 1498–1507. https://doi.org/10.1093/jme/tjz070 PMID: 31549726

109. Chaintoutis SC, Papa A, Pervanidou D, Dovas CI. Evolutionary dynamics of lineage 2 West Nile virus in Europe, 2004–2018: Phylogeny, selection pressure and phylogeography. Mol Phylogenet Evol. 2019; 141: 106617. https://doi.org/10.1016/j.ympev.2019.106617 PMID: 31521822

110. Armstrong PM, Vossbrinck CR, Andreadis TG, Anderson JF, Pesko KN, Newman RM, et al. Molecular evolution of West Nile virus in a northern temperate region: Connecticut, USA 1999–2008. Virology. 2011; 417: 203–210. https://doi.org/10.1016/j.virol.2011.06.006 PMID: 21723580

111. Amore G, Bertolotti L, Hamer GL, Kitron UD, Walker ED, Ruiz MO, et al. Multi-year evolutionary dynamics of West Nile virus in suburban Chicago, USA, 2005–2007. Philos Trans R Soc B Biol Sci. 2010; 365: 1871–1878. https://doi.org/10.1098/rstb.2010.0054 PMID: 20478882

112. Aguilera-Sepúlveda P, Napp S, Llorente F, Solano-Manrique C, Molina-López R, Obón E, et al. West Nile Virus Lineage 2 Spreads Westwards in Europe and Overwinters in North-Eastern Spain (2017–2020). Viruses. 2022; 14: 569. https://doi.org/10.3390/v14030569 PMID: 35336976

113. Veo C, della Ventura C, Moreno A, Rovida F, Percivalle E, Canziani S, et al. Evolutionary Dynamics of the Lineage 2 West Nile Virus That Caused the Largest European Epidemic: Italy 2011–2018. Viruses. 2019; 11: 814. https://doi.org/10.3390/v11090814 PMID: 31484295

114. Duggal NK, Reisen WK, Fang Y, Newman RM, Yang X, Ebel GD, et al. Genotype-specific variation in West Nile virus dispersal in California. Virology. 2015; 485: 79–85. https://doi.org/10.1016/j.virol.2015.07.004 PMID: 26210076

115. Sotelo E, Fernández-Pinero J, Llorente F, Vázquez A, Moreno A, Agüero M, et al. Phylogenetic relationships of Western Mediterranean West Nile virus strains (1996–2010) using full-length genome sequences: single or multiple introductions? J Gen Virol. 2011; 92: 2512–2522. https://doi.org/10.1099/vir.0.033829-0 PMID: 21775579

116. Zehender G, Veo C, Ebranati E, Carta V, Rovida F, Percivalle E, et al. Reconstructing the recent West Nile virus lineage 2 epidemic in Europe and Italy using discrete and continuous phylogeography. Paraskevis D, editor. PLOS ONE. 2017; 12: e0179679. https://doi.org/10.1371/journal.pone.0179679 PMID: 28678837

117. Monaco F, Savini G, Calistri P, Polci A, Pinoni C, Bruno R, et al. 2009 West Nile disease epidemic in Italy: First evidence of overwintering in Western Europe? Res Vet Sci. 2011; 91: 321–326. https://doi.org/10.1016/j.rvsc.2011.01.008 PMID: 21334703

118. Sutherland WJ. Evidence for Flexibility and Constraint in Migration Systems. J Avian Biol. 1998; 29: 441. https://doi.org/10.2307/3677163

119. Dufour P, de Franceschi C, Doniol-Valcroze P, Jiguet F, Guéguen M, Renaud J, et al. A new westward migration route in an Asian passerine bird. Curr Biol. 2021; 31: 5590–5596.e4. https://doi.org/10.1016/j.cub.2021.09.086 PMID: 34687610

120. Cotton PA. Avian migration phenology and global climate change. Proc Natl Acad Sci. 2003; 100: 12219–12222. https://doi.org/10.1073/pnas.1930548100 PMID: 14519854

121. Zaifman J, Shan D, Ay A, Jimenez AG. Shifts in Bird Migration Timing in North American Long-Distance and Short-Distance Migrants Are Associated with Climate Change. Int J Zool. 2017; 2017: 1–9. https://doi.org/10.1155/2017/6025646

122. Rosenberg KV, Dokter AM, Blancher PJ, Sauer JR, Smith AC, Smith PA, et al. Decline of the North American avifauna. Science. 2019; 366: 120–124. https://doi.org/10.1126/science.aaw1313 PMID: 31604313

123. Trautmann S. Climate Change Impacts on Bird Species. In: Tietze DT, editor. Bird Species. Cham: Springer International Publishing; 2018. pp. 217–234. https://doi.org/10.1007/978-3-319-91689-7_12

124. Lemoine N, Schaefer H-C, Böhning-Gaese K. Species richness of migratory birds is influenced by global climate change. Glob Ecol Biogeogr. 2007; 16: 55–64. https://doi.org/10.1111/j.1466-8238.2006.00252.x

125. Remisiewicz M, Underhill LG. Large-Scale Climatic Patterns Have Stronger Carry-Over Effects than Local Temperatures on Spring Phenology of Long-Distance Passerine Migrants between Europe and Africa. Animals. 2022; 12: 1732. https://doi.org/10.3390/ani12131732 PMID: 35804633

126. McLean N, Kruuk LEB, van der Jeugd HP, Leech D, van Turnhout CAM, van de Pol M. Warming temperatures drive at least half of the magnitude of long-term trait changes in European birds. Proc Natl Acad Sci. 2022; 119: e2105416119. https://doi.org/10.1073/pnas.2105416119 PMID: 35238646

127. Myer MH, Johnston JM. Spatiotemporal Bayesian modeling of West Nile virus: Identifying risk of infection in mosquitoes with local-scale predictors. Sci Total Environ. 2019; 650: 2818–2829. https://doi.org/10.1016/j.scitotenv.2018.09.397 PMID: 30373059

128. Farooq Z, Rocklöv J, Wallin J, Abiri N, Sewe MO, Sjödin H, et al. Artificial intelligence to predict West Nile virus outbreaks with eco-climatic drivers. Lancet Reg Health—Eur. 2022; 17: 100370. https://doi.org/10.1016/j.lanepe.2022.100370 PMID: 35373173

129. Ewing DA, Purse BV, Cobbold CA, White SM. A novel approach for predicting risk of vector-borne disease establishment in marginal temperate environments under climate change: West Nile virus in the UK. J R Soc Interface. 2021; 18: 20210049. https://doi.org/10.1098/rsif.2021.0049 PMID: 34034529

130. Fasano A, Riccetti N, Angelou A, Gomez-Ramirez J, Ferraccioli F, Kioutsioukis I, et al. An epidemiological model for mosquito host selection and temperature-dependent transmission of West Nile virus. Sci Rep. 2022; 12: 19946. https://doi.org/10.1038/s41598-022-24527-5 PMID: 36402904

131. Paull SH, Horton DE, Ashfaq M, Rastogi D, Kramer LD, Diffenbaugh NS, et al. Drought and immunity determine the intensity of West Nile virus epidemics and climate change impacts. Proc R Soc B Biol Sci. 2017; 284: 20162078. https://doi.org/10.1098/rspb.2016.2078 PMID: 28179512

132. Keyel AC, Raghavendra A, Ciota AT, Elison Timm O. West Nile virus is predicted to be more geographically widespread in New York State and Connecticut under future climate change. Glob Change Biol. 2021; 27: 5430–5445. https://doi.org/10.1111/gcb.15842 PMID: 34392584

133. Beeman SP, Morrison AM, Unnasch TR, Unnasch RS. Ensemble ecological niche modeling of West Nile virus probability in Florida. Silva D de P, editor. PLOS ONE. 2021; 16: e0256868. https://doi.org/10.1371/journal.pone.0256868 PMID: 34624026

134. Cuervo PF, Artigas P, Mas-Coma S, Bargues MD. West Nile virus in Spain: Forecasting the geographical distribution of risky areas with an ecological niche modelling approach. Transbound Emerg Dis. 2022; 69. https://doi.org/10.1111/tbed.14398 PMID: 34812589

135. Sofia M, Giannakopoulos A, Giantsis IA, Touloudi A, Birtsas P, Papageorgiou K, et al. West Nile Virus Occurrence and Ecological Niche Modeling in Wild Bird Species and Mosquito Vectors: An Active Surveillance Program in the Peloponnese Region of Greece. Microorganisms. 2022; 10: 1328. https://doi.org/10.3390/microorganisms10071328 PMID: 35889046

136. Marcantonio M, Rizzoli A, Metz M, Rosà R, Marini G, Chadwick E, et al. Identifying the Environmental Conditions Favouring West Nile Virus Outbreaks in Europe. Gourbiere S, editor. PLOS ONE. 2015; 10: e0121158. https://doi.org/10.1371/journal.pone.0121158 PMID: 25803814

137. Marini G, Pugliese A, Wint W, Alexander NS, Rizzoli A, Rosà R. Modelling the West Nile virus force of infection in the European human population. One Health. 2022; 15: 100462. https://doi.org/10.1016/j.onehlt.2022.100462 PMID: 36532665

138. Bowman C, Gumel A, Vandendriessche P, Wu J, Zhu H. A mathematical model for assessing control strategies against West Nile virus. Bull Math Biol. 2005; 67: 1107–1133. https://doi.org/10.1016/j.bulm.2005.01.002 PMID: 15998497

139. Bhowmick S, Gethmann J, Conraths FJ, Sokolov IM, Lentz HHK. SEIR-Metapopulation model of potential spread of West Nile virus. Ecol Model. 2023; 476: 110213. https://doi.org/10.1016/j.ecolmodel.2022.110213

140. DeFelice NB, Schneider ZD, Little E, Barker C, Caillouet KA, Campbell SR, et al. Use of temperature to improve West Nile virus forecasts. Lessler J, editor. PLOS Comput Biol. 2018; 14: e1006047. https://doi.org/10.1371/journal.pcbi.1006047 PMID: 29522514

141. Di Pol G, Crotta M, Taylor RA. Modelling the temperature suitability for the risk of West Nile Virus establishment in European *Culex pipiens* populations. Transbound Emerg Dis. 2022; 69. https://doi.org/10.1111/tbed.14513 PMID: 35304820

142. Lourenço J, Barros SC, Zé-Zé L, Damineli DSC, Giovanetti M, Osório HC, et al. West Nile virus transmission potential in Portugal. Commun Biol. 2022; 5: 6. https://doi.org/10.1038/s42003-021-02969-3 PMID: 35013546

143. Angelou A, Kioutsioukis I, Stilianakis NI. A climate-dependent spatial epidemiological model for the transmission risk of West Nile virus at local scale. One Health. 2021; 13: 100330. https://doi.org/10.1016/j.onehlt.2021.100330 PMID: 34632040

144. García-Carrasco J-M, Muñoz A-R, Olivero J, Segura M, Real R. Predicting the spatio-temporal spread of West Nile virus in Europe. Camp J, editor. PLoS Negl Trop Dis. 2021; 15: e0009022. https://doi.org/10.1371/journal.pntd.0009022 PMID: 33411739

145. Wimberly MC, Lamsal A, Giacomo P, Chuang T-W. Regional Variation of Climatic Influences on West Nile Virus Outbreaks in the United States. Am J Trop Med Hyg. 2014; 91: 677–684. https://doi.org/10.4269/ajtmh.14-0239 PMID: 25092814

146. Paz S, Malkinson D, Green MS, Tsioni G, Papa A, Danis K, et al. Permissive Summer Temperatures of the 2010 European West Nile Fever Upsurge. Mores CN, editor. PLoS ONE. 2013; 8: e56398. https://doi.org/10.1371/journal.pone.0056398 PMID: 23431374

147. Mihailović DT, Petrić D, Petrović T, Hrnjaković-Cvjetković I, Djurdjevic V, Nikolić-orić E, et al. Assessment of climate change impact on the malaria vector Anopheles hyrcanus, West Nile disease, and incidence of melanoma in the Vojvodina Province (Serbia) using data from a regional climate model. Samy AM, editor. PLOS ONE. 2020; 15: e0227679. https://doi.org/10.1371/journal.pone.0227679 PMID: 31940403

148. Harrigan RJ, Thomassen HA, Buermann W, Smith TB. A continental risk assessment of West Nile virus under climate change. Glob Change Biol. 2014; 20: 2417–2425. https://doi.org/10.1111/gcb.12534 PMID: 24574161

149. Azmi K, Tirosh-Levy S, Manasrah M, Mizrahi R, Nasereddin A, Al-Jawabreh A, et al. West Nile Virus: Seroprevalence in Animals in Palestine and Israel. Vector-Borne Zoonotic Dis. 2017; 17: 558–566. https://doi.org/10.1089/vbz.2016.2090 PMID: 28628400

150. Sánchez-Gómez A, Amela C, Fernández-Carrión E, Martínez-Avilés M, Sánchez-Vizcaíno JM, Sierra-Moros MJ. Risk mapping of West Nile virus circulation in Spain, 2015. Acta Trop. 2017; 169: 163–169. https://doi.org/10.1016/j.actatropica.2017.02.022 PMID: 28212847

151. Wang G, Minnis RB, Belant JL, Wax CL. Dry weather induces outbreaks of human West Nile virus infections. BMC Infect Dis. 2010; 10: 38. https://doi.org/10.1186/1471-2334-10-38 PMID: 20181272

152. Landesman WJ, Allan BF, Langerhans RB, Knight TM, Chase JM. Inter-Annual Associations Between Precipitation and Human Incidence of West Nile Virus in the United States. Vector-Borne Zoonotic Dis. 2007; 7: 337–343. https://doi.org/10.1089/vbz.2006.0590 PMID: 17867908

153. Shaman J, Day JF, Stieglitz M. Drought-Induced Amplification and Epidemic Transmission of West Nile Virus in Southern Florida. J Med Entomol. 2005; 42: 134–141. https://doi.org/10.1093/jmedent/42.2.134 PMID: 15799522

154. Shaman J, Day JF, Komar N. Hydrologic Conditions Describe West Nile Virus Risk in Colorado. Int J Environ Res Public Health. 2010; 7: 494–508. https://doi.org/10.3390/ijerph7020494 PMID: 20616987

155. Myer MH, Campbell SR, Johnston JM. Spatiotemporal modeling of ecological and sociological predictors of West Nile virus in Suffolk County, NY, mosquitoes. Ecosphere. 2017; 8. https://doi.org/10.1002/ecs2.1854 PMID: 30147987

156. Lu L, Zhang F, Oude Munnink BB, Munger E, Sikkema RS, Pappa S, et al. West Nile Virus spread in Europe—phylogeographic pattern analysis and key drivers. Evolutionary Biology; 2022 Nov. https://doi.org/10.1101/2022.11.10.515886

157. Giesen C, Herrador Z, Fernandez-Martinez B, Figuerola J, Gangoso L, Vazquez A, et al. A systematic review of environmental factors related to WNV circulation in European and Mediterranean countries. One Health. 2023; 16: 100478. https://doi.org/10.1016/j.onehlt.2022.100478

158. van Daalen KR, Romanello M, Rocklöv J, Semenza JC, Tonne C, Markandya A, et al. The 2022 Europe report of the Lancet Countdown on health and climate change: towards a climate resilient future. Lancet Public Health. 2022; S2468266722001979. https://doi.org/10.1016/S2468-2667(22)00197-9 PMID: 36306805

159. Farooq Z, Sjödin H, Semenza JC, Tozan Y, Sewe MO, Wallin J, et al. European projections of West Nile virus transmission under climate change scenarios. One Health. 2023; 16: 100509. https://doi.org/10.1016/j.onehlt.2023.100509

160. Chen C, Jenkins E, Epp T, Waldner C, Curry P, Soos C. Climate Change and West Nile Virus in a Highly Endemic Region of North America. Int J Environ Res Public Health. 2013; 10: 3052–3071. https://doi.org/10.3390/ijerph10073052 PMID: 23880729

161. Belova A, Mills D, Hall R, Juliana ASt, Crimmins A, Barker C, et al. Impacts of Increasing Temperature on the Future Incidence of West Nile Neuroinvasive Disease in the United States. Am J Clim Change. 2017; 06: 166–216. https://doi.org/10.4236/ajcc.2017.61010

162. Tran A, L'Ambert G, Balança G, Pradier S, Grosbois V, Balenghien T, et al. An Integrative Eco-Epidemiological Analysis of West Nile Virus Transmission. EcoHealth. 2017; 14: 474–489. https://doi.org/10.1007/s10393-017-1249-6 PMID: 28584951

163. Bartlow AW, Manore C, Xu C, Kaufeld KA, Del Valle S, Ziemann A, et al. Forecasting Zoonotic Infectious Disease Response to Climate Change: Mosquito Vectors and a Changing Environment. Vet Sci. 2019; 6: 40. https://doi.org/10.3390/vetsci6020040 PMID: 31064099

164. Alley RB, Emanuel KA, Zhang F. Advances in weather prediction. Science. 2019; 363: 342–344. https://doi.org/10.1126/science.aav7274 PMID: 30679358

165. Moran KR, Fairchild G, Generous N, Hickmann K, Osthus D, Priedhorsky R, et al. Epidemic Forecasting is Messier Than Weather Forecasting: The Role of Human Behavior and Internet Data Streams in Epidemic Forecast. J Infect Dis. 2016; 214: S404–S408. https://doi.org/10.1093/infdis/jiw375 PMID: 28830111

166. mosquitoalert.com. Mosquito Alert Home Page. 2022 [cited 10 Nov 2022]. Available from: http://www.mosquitoalert.com/en/

167. GBIF.org. GBIF Home Page. 2022 [cited 10 Nov 2022]. Available from: https://www.gbif.org/

168. Sullivan BL, Wood CL, Iliff MJ, Bonney RE, Fink D, Kelling S. eBird: A citizen-based bird observation network in the biological sciences. Biol Conserv. 2009; 142: 2282–2292. https://doi.org/10.1016/j.biocon.2009.05.006

169. Kays R, Davidson SC, Berger M, Bohrer G, Fiedler W, Flack A, et al. The Movebank system for studying global animal movement and demography. Methods Ecol Evol. 2022; 13: 419–431. https://doi.org/10.1111/2041-210X.13767

170. Parham PE, Waldock J, Christophides GK, Hemming D, Agusto F, Evans KJ, et al. Climate, environmental and socio-economic change: weighing up the balance in vector-borne disease transmission. Philos Trans R Soc B Biol Sci. 2015; 370: 20130551. https://doi.org/10.1098/rstb.2013.0551 PMID: 25688012

171. Cuddington K, Fortin M-J, Gerber LR, Hastings A, Liebhold A, O'Connor M, et al. Process-based models are required to manage ecological systems in a changing world. Ecosphere. 2013; 4: art20. https://doi.org/10.1890/ES12-00178.1

172. Vogels CBF, Hartemink N, Koenraadt CJM. Modelling West Nile virus transmission risk in Europe: effect of temperature and mosquito biotypes on the basic reproduction number. Sci Rep. 2017; 7: 5022. https://doi.org/10.1038/s41598-017-05185-4 PMID: 28694450

173. Bradley CA, Altizer S. Urbanization and the ecology of wildlife diseases. Trends Ecol Evol. 2007; 22: 95–102. https://doi.org/10.1016/j.tree.2006.11.001 PMID: 17113678

174. White RJ, Razgour O. Emerging zoonotic diseases originating in mammals: a systematic review of effects of anthropogenic land-use change. Mammal Rev. 2020; 50: 336–352. https://doi.org/10.1111/mam.12201 PMID: 32836691

175. Harrigan RJ, Thomassen HA, Buermann W, Cummings RF, Kahn ME, Smith TB. Economic Conditions Predict Prevalence of West Nile Virus. Getz WM, editor. PLoS ONE. 2010; 5: e15437. https://doi.org/10.1371/journal.pone.0015437 PMID: 21103053

176. Liu H, Weng Q. An examination of the effect of landscape pattern, land surface temperature, and socioeconomic conditions on WNV dissemination in Chicago. Environ Monit Assess. 2009; 159: 143–161. https://doi.org/10.1007/s10661-008-0618-6 PMID: 19107566

177. Lockaby G, Noori N, Morse W, Zipperer W, Kalin L, Governo R, et al. Climatic, ecological, and socioeconomic factors associated with West Nile virus incidence in Atlanta, Georgia, U.S.A. J Vector Ecol. 2016; 41: 232–243. https://doi.org/10.1111/jvec.12218 PMID: 27860011

178. CDC. One Health. 2022 Nov 7 [cited 10 Nov 2022]. Available from: https://www.cdc.gov/onehealth/index.html

179. Marchino M, Paternoster G, Favretto AR, Balduzzi G, Berezowski J, Tomassone L, et al. Process evaluation of integrated West Nile virus surveillance in northern Italy: an example of a One Health approach in public health policy. Eval Program Plann. 2021; 89: 101991. https://doi.org/10.1016/j.evalprogplan.2021.101991 PMID: 34493380

180. Khan MS, Rothman-Ostrow P, Spencer J, Hasan N, Sabirovic M, Rahman-Shepherd A, et al. The growth and strategic functioning of One Health networks: a systematic analysis. Lancet Planet Health. 2018; 2: e264–e273. https://doi.org/10.1016/S2542-5196(18)30084-6 PMID: 29880158