

Temperature Effects on the Basic Reproductive Number (R₀) Of West Nile Virus, Based On Ecological Parameters: Endemic Vs. New Emergence Regions

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Abstract

This study is to compare the Basic Reproduction Number of West Nile Virus in new-emergence regions to that of endemic ones, given that there is global warming and that R_0 is a function of temperature sensitive parameters. It has been suggested that elevated temperatures via global warming affect the spread of vector-borne diseases. West Nile virus (WNV), an arbovirus, is transmitted to hosts mainly by mosquitoes of the genera *Culex*, and amplified through an enzootic cycle where mostly birds are the reservoir. Parameters involved in the amplification are temperature sensitive, thus we compare endemic to new-emergence regions for their susceptibility to West Nile Virus (WNV) based on their basic reproductive number (R_0) which is a complex function of temperature dependent parameters. R_0 for West Nile Virus indicates that new emergence regions are more vulnerable to outbreaks than endemic regions; that once introduced WNV will spread there more rapidly even in lower temperatures. The analysis suggests that the high susceptibility of birds in new emergence areas along with temperature sensitive parameters related to the vector, may explain in a complex manner, the higher WNV propagation in these regions, as it is happening in North and Central America.

Keywords: Eco-epidemiology; West Nile Virus; Basic reproductive number; Global warming

Introduction

West Nile virus (WNV), an arbovirus of the genus *Flavivirus* and the family *Flaviviridae*, was first recognized in 1937 after its isolation from a native of Uganda [1]. It is transmitted to hosts mainly by mosquitoes of the genera *Culex*; although *Aedes*, and others have been also involved in selected geographic locations [2,3]. Already in the 1950s birds were identified as the main reservoirs of WNV in the Nile delta [4,5] and later confirmed in other part of the world [6-8]. In the USA, birds such as geese, pigeons, crows, blue jays and house sparrows were found to be infected with WNV [7]. It has been suggested that robins may serve as a primary amplifying host of the virus, and develop a high-level of viremia that lasts for several days [9]. During the viremia period, adult female mosquitoes may get infected via a blood meal they take, and pass the infection to not yet infected birds. Thus, the infection circulates in nature in an enzootic cycle within bird reservoirs; humans and other mammals are affected mainly as dead-end hosts as they do not contribute to the amplification of the virus [10-12].

Epidemiology and ecology

In 1994 to 1999, WNV emerged in temperate regions of Europe, North Africa and North America, presenting a threat to public health, as well as equine and avian health [8,12]. Although about 80% of people infected with WNV are asymptomatic, and only about 1% progress to severe disease, some might seriously be affected with neurological complications or death [13,14]. Outbreaks were reported in Algeria in 1994, Romania 1996-1997, the Czech Republic in 1997, the Democratic Republic of Congo in 1998, Russia in 1999, and the USA in 1999 [6,14-18]. During 1999-2006, the WNV extended its range throughout the new world and is expected to continue to expand [3,10,19-21]. Migratory birds are thought to participate in the geographical spread of the virus in North America [6,22].

However the virus, affecting humans and circulating within avian reservoirs was already recognized in the middle of last century. The first outbreak of the virus in Israel and Egypt occurred in the 1950s

[4,5,23]. In 1980, an outbreak was reported in southern Israel [24,25] followed by a major outbreak in the year 2000 [26-28]. The main mosquito vectors in Israel and Egypt are *Culex perexiguus* [29-31] and *C. pipiens* [4,32]. Typically wild birds are the principal reservoir of the West Nile virus. The virus has been isolated from a number of wetland and terrestrial avian species including migratory birds such as the barred warbler, turtledove, pigeons, wagtails, geese and white storks [31,33]. Some of these birds play an important role in intercontinental transmission [34]. This may be due to sufficiently prolonged viremia as was documented in several bird species. Such prolonged viremia is likely to occur during migration because of its substantial physiologic stress on birds. Outbreaks of the virus occur during late summer or early fall, coinciding with the arrival of large concentrations of migratory birds and with elevated mosquito population. Indeed, WNV was isolated from migrating white storks that landed in Eilat, Israel in 1998 [33]; the flock migrated southward for the first time and had not previously flown over Israel. It was suggested that the storks became infected in Europe prior to the time of migration [33]. It is also likely that the virus is carried by the migration of birds in the spring, from Africa to European breeding grounds via Israel as a transit and resting-place [35]. Supporting the hypothesis that migratory birds play a role in the geographic spread of the virus, the finding that WNV isolated from *Culex perexiguus* caught along the Kenya-Uganda border in the spring of 1998, demonstrated a high similarity with a *Culex pipiens*

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mosquito isolate from Romania in 1996 [36]. Although migratory birds are considered an important factor in the geographic spread of WNV and its introduction in new geographic locations, most probably the domestic ones are those involved in its amplification cycle [4,5].

Endemic vs. New-emergence regions

The seminal study of Work et al (1955) on WNV from the Nile Delta, developed the concept of non-endemic, transitional and endemic zones. It was argued that differences in the various environmental components among these zones accounted for differences in the persistence of the virus. In this paper, we use the Basic Reproduction Number, R_0 , derived from a formula based on ecological properties of the various components of the transmission cycle, to compare the risk of WNV in Israel which emerged in the 1950s, thus considered an endemic region, to that of North America, where the virus emerged in 1999, thus considered a new-emergent region [10,14]. The assumption is that similar mosquito species are involved in the two regions and they also share an almost genetically identical viral strains, suggesting that the infection in the US may have originated in Israel [37]. Recent work demonstrated that the virus in North America has been evolving and is now more efficient at disseminating through a mosquito [38].

The hypothesis is that the progression of the epidemic in these two zones will differ according to their sensitivity to environmental components as captured by the equation of the Basic Reproductive Number, R_0 , defined as the expected number of infected birds originated by one infected bird in the population, presented in Figure 1.

Thus, we use R_0 to compare the vulnerability of these two zones as a function of temperature, as there are yearly variations and because of predictions of systematic global warming. In addition, it is anticipated that climate changes associated with global warming will have an effect particularly on vector-borne diseases such as WNV [39] and their spread to new zones [40]. Such a direct effect of elevated temperature on WNV has already been seen in parts of Russia and Israel [41].

The Basic reproductive number, R_0

It has been observed experimentally that WNV transmission depends on entomological factors related to the interaction of mosquitoes with its reservoir and also to the level of immunity of this reservoir [42]. The high level of complexity involved in WNV spread is captured by the basic reproductive number, R_0 (Figure 1).

In the process of elucidating the role of mosquitoes in the transmission of malaria, Ross constructed the first mathematical model for describing epidemics [43]. Ross's model was expanded by Macdonald (1957) and by other researchers to model other vector-borne diseases [44]. One of the basic results of the analysis of the Ross-Macdonald model is the derivation of the basic reproductive number R_0 for malaria in terms of entomological parameters related to mosquitoes. R_0 is the number of secondary cases arising from a single case in a susceptible population, and depends on ecological variables [45], one of which is the duration of the infectious period within the reservoir ("see equation in Figure 1") [46]. Once the infection agent is introduced $R_0 > 1$, the disease will propagate. When $R_0 < 1$, the infection cannot be sustained. In the case of malaria, for which the concept was originally developed, humans are not only severely affected hosts but also reservoirs and participants in the infection cycle. However, the concept of R_0 was later used to explore the potential for the rise and fall of other infectious diseases with different modes of transmission and non-human reservoir [47]. Recently, R_0 was specifically derived for WNV from a system of nine ordinary differential equations model

that linked bird-reservoirs with mosquito-vectors and human hosts. Although humans were included in the model, a qualitative analysis of the equations system rendered the result, that for a certain threshold of R_0 , depending on parameters related only to the mosquito-bird cycle, its value could be less than a unit and, thus in principle, WNV could be eradicated [48].

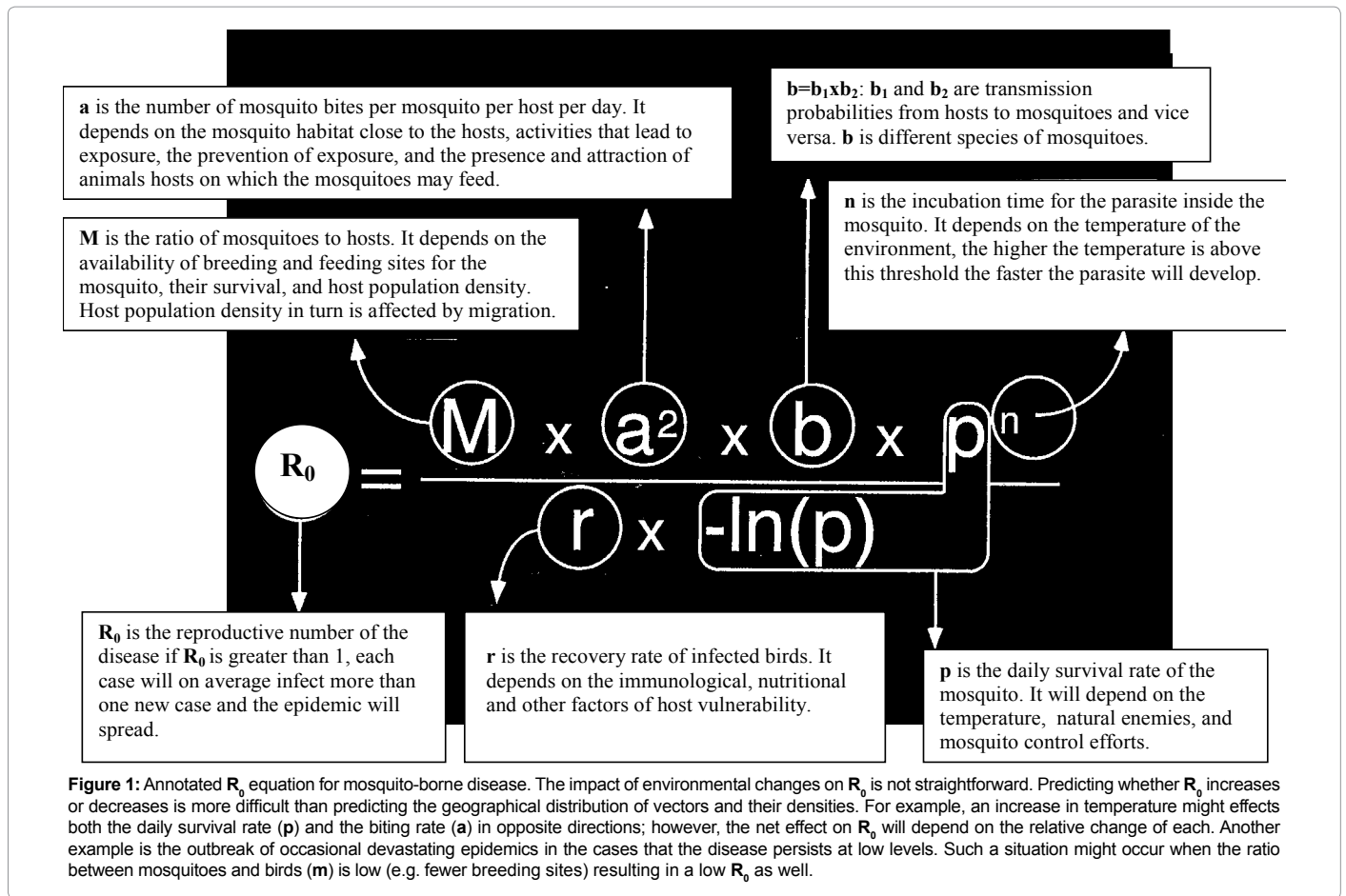
Material and Methods

In our work, we use the original definition of R_0 as presented in Figure 1 focusing only on the bird-mosquito cycle, which is relevant for virus amplification. The annotated equation Figure 1 includes definitions of the ecological parameters and their dependence on environmental factors.

Calculations for R_0 as a function of temperature in endemic region (e.g., Israel and Egypt) vs. new emergence region (e.g., North America) are based on various parameter estimates from the literature and presented in Table 1 [4,5,34,49-53]. The entomological parameters pertain to species of the genera *Culex* and *Aedes*, which are the main species involved in WNV transmission. The probability that an infected mosquito will transmit the infection (b_1) is 0.9 for both locations in temperatures between 23 to 35°C, 0.4 at 20°C 0.3 at 18°C and 0.8 at 22°C [50,51,54-57]. However, the probability that an infected bird will transmit the infection (b_2) is a lot higher in new emergence region since WNV is rather new and most of the birds are susceptible to the virus and will develop high viremia. In endemic area the majority of the birds are likely to be resistant and non-infectious [4,58]. It is more likely that juvenile birds that have not yet been exposed to the virus will be more susceptible to infection and, therefore, more infections and become an important component of the WNV amplification cycle [4,59]. Thus, we chose as a preliminary estimate: $b_2=0.2$ in endemic region and $b_2=0.8$ in new emergence region. These estimates are based on the work of Work et al (1955), showing that in endemic areas percentage of sero-positive birds vary from 40% to 100% with average of 77%. They further describe different levels of WNV prevalence according to immunity of hooded crows; non-endemic with 1% immunity, transition area with 31% immunity and endemic with 80% immunity. In non-endemic areas where the virus has more recently been spreading and there has not been enough time for genetic adaptation in the birds, it was found that neutralizing antibodies were detected in 23% of the resident birds in Staten Island [7] and specific anti-WNV antibodies were detected in 21% of the resident birds in the Dominican Republic [60]. In addition, WNV neutralizing antibodies in human populations showed that in non-endemic area there is 24% immunity and in endemic area 84% immunity [5]. There is not sufficient data for an accurate estimate of the number of mosquitoes per bird (m), however, we assume as a first approximation that the number increases as a function of temperature as presented in Table 1. In any case, we estimate that m and the other parameters (a , p and n) will vary similarly in both regions. The average recovery rate (r) in birds was estimated to be 0.25 since the average incubation period of WNV in a bird is thought to be about 4 days [7]. The range of temperatures was chosen to represent the entomological characteristics of transmission and mosquito's survival.

Results and Discussion

In Figure 2 a graph of R_0 as a function of temperature for both endemic and new-emergence regions is presented. Sensitivity analysis for 10% variation in temperature did not change the main result that at elevated temperatures, the new-emergence region is more susceptible to outbreaks. While in endemic regions, the values of R_0 stay closer to one. When $R_0 < 1$, the WNV epidemic cannot be sustained as can be seen



in endemic regions at a temperature that will promote on the other hand, the propagation of the virus in new-emergence regions. According to this analysis, the higher susceptibility of birds in new emergence areas may effect, in a complex manner, the more accelerated WNV propagation in these regions. Assuming that North America is considered to be a new-emergence area, according to the WNV R_0 model, taking into account its qualitative nature, WNV will propagate there within bird populations, starting already at 25°C. In endemic regions, for example, WNV will start propagating at a temperature close to 30°C and at a lower rate. The model is irrelevant for temperature higher than 35°C due to mosquito mortality. Estimates of R_0 , as an indicator for WNV emergence, will be more accurate as we obtain more adequate parameter values to make better comparisons and identify locations at risk. On an annual level in the USA, there is a seasonal trend of human infection occurring from May to September – during the summer when the temperatures are obviously higher consistent with a higher R_0 for the amplification cycle at elevated temperatures. This is also consistent with the findings in New England in particular in Connecticut where field-collected mosquitoes showed a high virus activity extending from early August through the end of October [61]. Once WNV emerges, it is expected that it will continue to spread in the new world over the next years, introduced primarily via migratory birds and amplified by local domestic cycles. It is likely that this virus will propagate into Central and South America, as it has already started to happen [13].

New in the new world, WNV has continued to expand in the Western Hemisphere, and virus activity has been detected in Canada,

Mexico and the West Indies as well. “Health Canada” reported its first WNV isolation from birds in Ontario in 2001. Four hundred cases were identified in humans in Ontario and Quebec in 2002, and by the end of 2003, disease activity had spread to a total of nine provinces and territories [62].

A similar pattern of spread has been seen in the Caribbean and Central America: WNV-neutralizing antibodies were detected in samples from birds in the Caribbean Islands in 2002 and from horses in Mexico [60,63-65]. It is likely that once introduced to a new emergence area in the Western Hemisphere, WNV will become endemic as it already happened in the Middle East. Meanwhile, new-emergence regions are more vulnerable to spread of infection, as R_0 reaches a threshold of 1 at lower temperatures (Figure 2). It is clear that the expected increasing global warming will affect these regions a lot faster than the endemic ones. Although the biological components of the transmission cycle of a vector-borne disease are similar in different parts of the world, the patterns of spread differ from location to location depending on environmental conditions. Thus, as the world undergoes environmental change accompanied by global warming [66-68], the many factors contributing to the spread of vector-borne diseases, such as agricultural practices and land use will change as well [69,70]. The destruction of the natural surroundings (e.g., deforestation and desertification that accompany agricultural land development) might create new ecological conditions that will affect the distribution of birds and their penetration into new-emergence regions that, as we saw, are more susceptible to outbreaks. Here we use R_0 qualitatively to compare the spread of WNV in

Temperature (°C)	b1	b2: endemic region	b2: New-emergence region	m	a	p	n	r
18	0.3	0.2	0.8	3	0.7	0.9	30	0.25
20	0.4	0.2	0.8	5	0.8	0.9	20	0.25
22	0.8	0.2	0.8	6	0.9	0.9	15	0.25
23	0.9	0.2	0.8	10	1	0.9	15	0.25
25	0.9	0.2	0.8	15	1	0.9	13	0.25
25.5	0.9	0.2	0.8	16	1.1	0.9	15	0.25
26	0.9	0.2	0.8	17	1.2	0.9	10	0.25
27	0.9	0.2	0.8	18	1.3	0.9	10	0.25
29	0.9	0.2	0.8	19	1.4	0.9	10	0.25
30	0.9	0.2	0.8	25	1.5	0.9	10	0.25
31	0.9	0.2	0.8	24	1.6	0.9	10	0.25
32	0.9	0.2	0.8	28	1.8	0.85	10	0.25
33	0.9	0.2	0.8	32	1.9	0.85	10	0.25
34	0.9	0.2	0.8	36	2	0.8	10	0.25
35	0.9	0.2	0.8	40	2.2	0.8	10	0.25

Calculations for R_0 as a function of temperature in endemic region vs. new emergence region are based on various parameter estimates from the literature. **Table 1:** Parameters used to estimates WNV basic reproductive number (R_0)

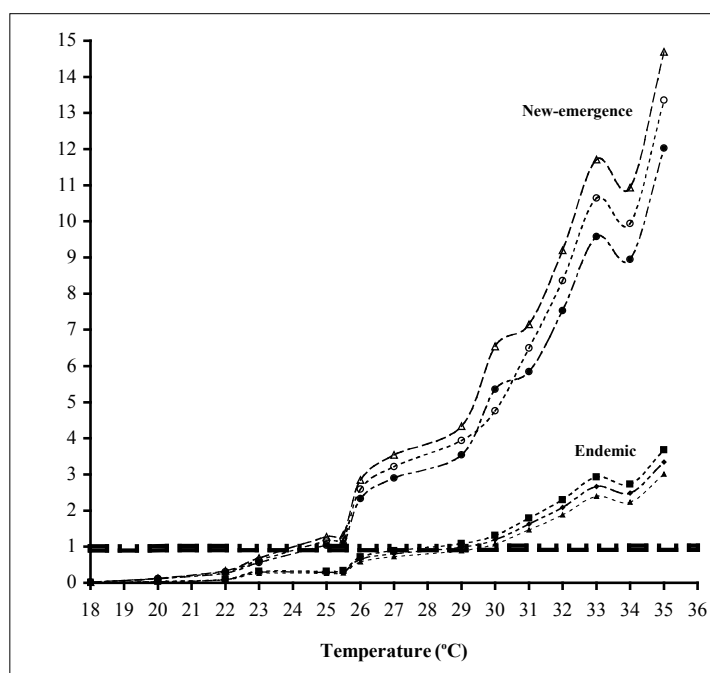


Figure 2: Basic reproduction number (R_0) for West Nile Virus in endemic region and in new emergence region (parameters used for R_0 calculation are presented in Table 1). R_0 presented as a function of temperature for both endemic and new-emergence regions with sensitivity analysis for 10% variation in temperatures.

endemic vs. new emerging regions.

The R_0 equation Figure 1 does not take into account other modes of transmission that might add to the amplification such as cloacal shedding of virus (found in 17 of 24 species), oral shedding in 12 of 14 species, contact and oral transmission [7] feather-picking of sick birds [71] and non-viremic transmission via vector co-feeding [72-74]. We assume that these modes of direct transmission are marginal; however, it might have implications if we want to control the disease through vector destruction. In this paper, we use R_0 solely as an effective way

to explain the rapid expansion of WNV in new emergence areas. The effect of temperature on some aspects of WNV is well characterized in the literature, mostly examining one parameter at a time in a laboratory setting. In the field the entomological parameters act together along with those of host competence, as described by the equation of the basic reproductive number (R_0) (Figure 1). Our estimates for infectivity of birds is based on published data as already described; moreover a 10% sensitivity analysis shows that the result is robust, that even a 10% deviation in our estimates will not change the main prediction

that new-emergence regions are more vulnerable to WNV spread as a consequence of climate warming (Figure 2). Indeed, the simulations of the Basic Reproduction Number (R0) as a function of temperature sensitive parameters, showing that geographic locations within new-emergence areas are more vulnerable to the spread of West Nile Virus, are consistent with the pattern of spread in the Caribbean and Central America. On the other hand the lower R0s in endemic areas are representative of the pattern of spread in Egypt and Israel. This approach might be valuable for future qualitatively comparisons of sites with different environmental parameters and predict regions at risk.

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