EcoHealth 5, 40–48, 2008
DOI: 10.1007/s10393-007-0150-0

EcoHealth



*Original Contribution*

# Influence of Warming Tendency on *Culex pipiens* Population Abundance and on the Probability of West Nile Fever Outbreaks (Israeli Case Study: 2001–2005)

Shlomit Paz and Iris Albersheim

*Department of Geography and Environmental Studies, University of Haifa, Abba Hushi Road, Mt. Carmel, Haifa 31905, Israel*

**Abstract:** Climate change and West Nile fever (WNV) are both subjects of global importance. Many mosquitoes and the diseases they carry, including West Nile virus (WNV), are sensitive to temperature increase. The current study analyzes the lag correlations between weather conditions (especially air temperature) and 1) *Culex pipiens* mosquito population abundance, and 2) WNF frequency in humans, between 2001 and 2005 in Israel. These 5 years follow a long period with a documented tendency for temperature increase in the hot season in the country. Monthly anomalies of minimum and maximum temperatures, relative seasonal rainfall contribution, mosquito samplings (hazard level), and WNF cases (hospital admission dates and patients' addresses) were analyzed. Logistic regression was calculated between the climatic data and the mosquito samples, as Spearman correlations and Pearson cross-correlations were calculated between daily temperature values (or daily precipitation amounts) and the hospital admission dates. It was found that the disease appearance reflects the population distribution, while the risk tends to escalate around the metropolis characterized by an urban heat island. Positive anomalies of the temperature during the study period appear to have facilitated the mosquito abundance and, consequently, the disease emergence in humans. An important finding is the potential influence of extreme heat in the early spring on the vector population increase and on the disease's appearance weeks later. Awareness of such situations at the beginning of the spring may help authorities to reduce the disease risk before it becomes a real danger.

**Keywords:** West Nile virus, Mosquitoes, *Culex pipiens*, Climate change

## Introduction

One of the most disturbing impacts of global warming is on human health, in various complex ways. The altered spatial distribution of some infectious disease vectors such as mosquitoes (IPCC, 2007a) has a considerable impact on the population.

Published online: February 12, 2008

*Correspondence to:* Shlomit Paz, e-mail: shlomit@geo.haifa.ac.il

Temperature change may increase the potential transmission of many vector-borne diseases carried by mosquitoes, such as malaria, dengue fever, and West Nile virus (WNV). This is because temperature is related to the life-cycle dynamics of both the vector species and the pathogenic organisms. Warming of the mosquito environment boosts their rates of reproduction and number of blood meals, prolongs their breeding season, and shortens the maturation period for the microbes they disperse (Reeves et al., 1994; Lindsay and Birle, 1996; Marsh and Gross, 2001; McMichael, 2003; Pats et al., 2003; Epstein, 2005; Tibbetts, 2007).

WNV is a member of the Japanese encephalitis serogroup, family Flaviviruses. The virus is transmitted between birds and transferred by carriers, especially by *Culex* mosquitoes. The WNV vectors in Israel are mosquitoes of the *Cx. pipiens* and *Cx. perexiguus* types (Weinberger et al., 2001). *Cx. pipiens*, the most widespread and abundant mosquito in Israel (Orshan et al., 2005), can be found in a fairly wide range of larval habitats, but is generally associated with water that has a high organic content. Most *Cx. pipiens* specimens require a blood meal that contains the nutrient necessary for egg development, and therefore bite birds (Snow, 1990; Byrne and Nichols, 1999).

The basic transmission cycle of WNV occurs in a rural ecosystem, involving wild birds as the principal hosts, and mosquitoes, largely bird-feeding species, as the primary vectors. Another cycle exists in an urban ecosystem (domestic birds and mosquitoes feeding on both birds and humans). The virus is amplified during periods of adult mosquito blood-meal feeding by continuous transmission between mosquitoes and susceptible bird species. Humans and horses are incidental and dead-end hosts for the viruses (Tsai et al., 1998; Hubalek and Halouzka, 1999; Epstein, 2001; Mclean et al., 2001; Gibbs et al., 2006; CDC, 2007).

West Nile fever (WNF) in humans appears after an incubation period of 3–15 days, mostly at the end of the summer (CDC, 2004). The virus was recognized as a cause of fatal human meningitis or encephalitis in elderly patients during an outbreak in Israel in 1957 (Spigland et al., 1958).

WNV is endemic in Africa, in southwestern Asia, in eastern and southern Europe, and in parts of the Mediterranean basin (Hayes et al., 1989; Hubalek and Halouzka, 1999; Tsai, 2001; Dohm et al., 2002). The virus was first detected in the western hemisphere in New York City in 1999 (Nash et al., 2001; Tibbetts, 2007). It has since moved rapidly westward and was detected in California in 2004 (Granwehr et al., 2004). Today, WNV exists also in Central and South America and in the Caribbean (Gibbs et al., 2006), and is therefore a vector-borne pathogen of global importance. It is worth noting that genetic analysis indicated that the strain responsible for the NYC 1999 outbreak was nearly identical to a strain that was circulating in Israel in 1998 (Lanciotti et al., 1999).

Various factors impact WNV transmission, epidemiology, and geographic distribution. However, environmental temperatures were found to influence vector competence for arboviruses in general, and WNV in particular (Jupp, 1974; Cornel et al., 1993). Warm conditions were detected as crucial causes of the outbreaks (Turell et al., 2001). It has been proven experimentally that high temperatures during incubation affect the transmission of WNV in Cx. *pipiens*: Dohm and Turell (2001) demonstrated the effect of simulated temperatures on WNV replication in *Cx. pipiens*, and Dohm et al. (2002) showed that infection rates are directly related to subsequent incubation temperature. Savage et al. (1999) found that summer temperature is one of the most important environmental variables modulating WNV activity in Europe.

In a study on the linkage between extreme heat and the WNF outbreak in Israel during summer 2000, Paz (2006) found that when air temperatures do not fall below 25°C for 7 days, the minimum temperature becomes the most important climatic factor in encouraging the earlier appearance of the disease. Since bird reservoirs sustain an infectious viremia (virus circulating in the bloodstream) for 1–4 days after exposure (then these hosts develop lifelong immunity), a sufficient number of vectors must feed on an infectious host to ensure that some survive long enough to feed again on a susceptible reservoir host (CDC, 2007). Therefore, when warm conditions with a high minimum temperature encourage mosquitoes' abundance (as reproduction rate) and activity (number of blood meals), the virus transmission potential may increase.

As Israel is located along the Syrian-African Rift, it is a major stopover for huge flocks of migrating birds, especially during the transition seasons. Since wild birds are the reservoir of WNV, this geographical location is crucial for disease transfer. Indeed, in recent years, the virus was detected in Israel in a large variety of birds (ICDC website 2004) that frequently interact with mosquitoes in areas of standing water.

Several WNF outbreaks were reported in Israel in the 1950s and one in 1980, but, by the end of the 20th Century, it was a forgotten disease. After a long absence, WNV was diagnosed in goose flocks in summer 1998. In summer 1999, 3 cases of WNV were reported in humans (2 deaths) and, in 2000, a large outbreak occurred with 429 cases (35 deaths), between August and November (ICDC website 2004). This outbreak occurred after summers of both medical and climatic warning signs. The three previous summers of 1998, 1999, and 2000 had the hottest ever recorded temperatures, with long heat waves (Bin et al., 2001; Paz, 2006). It is interesting to note that the development of the Israeli outbreak in summer 2000 was comparable to the cases in the Danube Valley in Romania (1996) and in NYC

(1999). Despite the climatic dissimilarity between the three regions, all are characterized by warm and humid summers. Each of the three outbreaks appeared after a long period of intense heat (Paz, 2006).

Recent studies observed several impacts of climate change in Israel, as well as in the whole eastern Mediterranean basin. During the second half of the 20th Century, an increase in the minimum and maximum summer temperature was detected (Ben-Gai et al., 1999). Heat waves have increased in frequency and severity (Saaroni et al., 2003; Paz, 2006; Paz et al., 2007). A tendency for drought was identified (Alpert et al., 2002; Paz et al., 2003; IPCC, 2007b) with an increase in the uncertain behavior of the precipitation patterns (Paz and Kutiel, 2003).

The current research aims to analyze the lag linkages between weather conditions (especially air temperature) and 1) *Culex pipiens* mosquito population abundance, and 2) WNF frequency in humans, under a documented tendency for temperature increase in the hot season in Israel. The study is based on the period from 2001 to 2005.

## Materials and Methods

### Data

All reported cases of WNF in Israel (date of admission and patients' address) during the years 2000–2005 were serologically confirmed by the Israeli Central Virology Laboratory (Data source: Israel Ministry of Health, Epidemiology Department, WNV database 2006). Data was collected from all 16 districts officially defined by the Israel Ministry of Health, from the north to the south of the country.

Weather data for the period of 2001–2005 in selected meteorological stations characterized all Israeli sub-climatic regions—12 stations for daily temperature (mean, minimum, and maximum) and 14 stations for daily rainfall amounts (Data source: Israel Meteorological Service [IMS]). These data were gathered in order to identify possible climatic conditions that could influence *Culex pipiens* population abundance and WNF distribution.

Data of mosquito samplings, generally *Culex pipiens* mosquito (the most common species in urban and rural areas of Israel; Orshan et al., 2005), on chosen dates throughout the years 2001–2005, were gathered at selected stations (near the meteorological stations), covering all districts throughout the country. The samples were collected by the Department of Pest Prevention of the Israel Ministry of Environmental Protection. After the mosquitoes were counted in the laboratory, the samples were classified according to three categories of increasing severity: 0 = no mosquito hazard, 1 = medium hazard (a few or dozens of mosquitoes), and 2 = severe hazard (hundreds of mosquitoes or more).

### Methods

WNF cases (date of admission and patients' address) were mapped using Geographic Information System (GIS) for the years 2000–2005.

Monthly anomalies of mean monthly temperatures (maximum and minimum) from the perennial monthly averages (maximum and minimum) of the period 1981–2000 for March (end of winter), May (spring), and August (summer), were calculated for selected stations, and characterized all Israeli sub-climatic regions. Selected months were mapped using GIS.

The relative percentage contribution of seasonal rainfall from the seasonal perennial averages of the period 1971–2000 for winter and spring was calculated.

The distribution of mosquito hazard levels was analyzed using GIS in selected stations throughout the country.

To identify lag correlations between weather conditions and mosquito hazard levels throughout the study period, multinomial logistic regression was calculated between daily temperatures (mean, minimum, and maximum) or daily precipitation amounts, and the mosquito hazard samplings. It is important to note that multinomial logistic regression is used with a categorical dependent variable (mosquito hazard category) that has more than two categories. The regression was computed for four main districts from the north to the south: a) northern Israel; b) Hadera region (~45 km north of Tel Aviv); c) Tel Aviv metropolis; and d) Beer Sheba district. More southerly areas were not analyzed due to population sparseness.

Spearman correlation was calculated between WNF cases (hospital admission dates) and mean daily temperatures/daily precipitation amounts, throughout the years 2001–2005. This was to identify linkages and lag correlations between weather conditions and WNF morbidity.

Pearson cross-correlations were calculated between daily minimum, maximum, and mean temperatures (or daily precipitation amounts) and the hospital admission dates in the Tel Aviv metropolis (the region with the highest number of WNF cases) in 2005 (the year with the highest disease distribution).

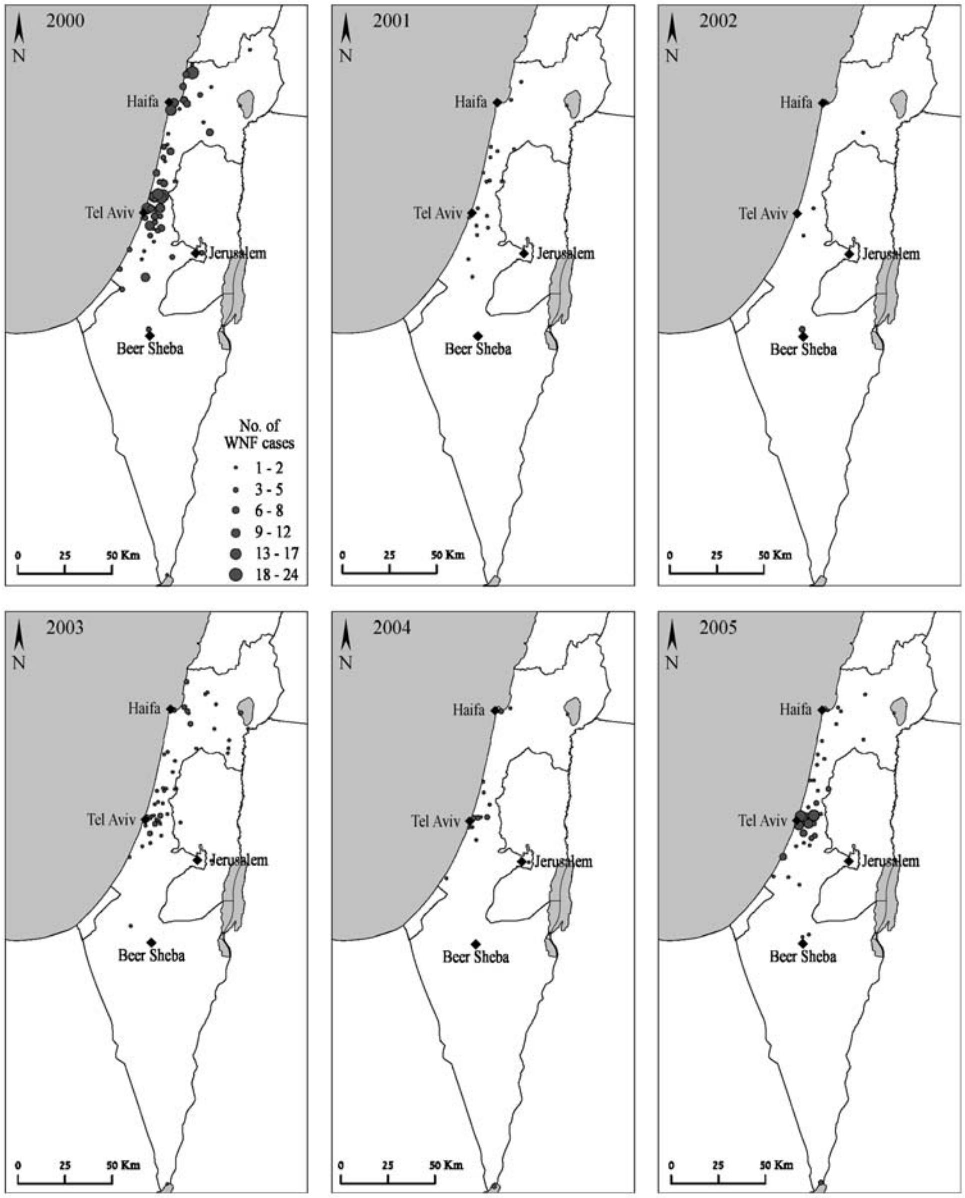


**Figure 1.** WNF case distribution in Israel, during the years 2000 (initial outbreak with 429 cases in humans), 2001 (33 cases), 2002 (7 cases), 2003 (80 cases), 2004 (38 cases), and 2005 (163 cases).

## Results

### WNF Distribution

Mapping of the geographical distribution of WNF in Israel throughout the years 2000–2005 (Fig. 1) indicated that the majority of cases occurred in the densely populated area (Tel Aviv metropolis) along the seashore, and less in the north, which is less populated. These results reflect the country's population dispersion.

### Temperature Increase

The warming tendency detected in the Israeli hot season in past decades (e.g., Ben-Gai et al., 1999; Paz et al., 2007) was ongoing in the current study period. A clear positive

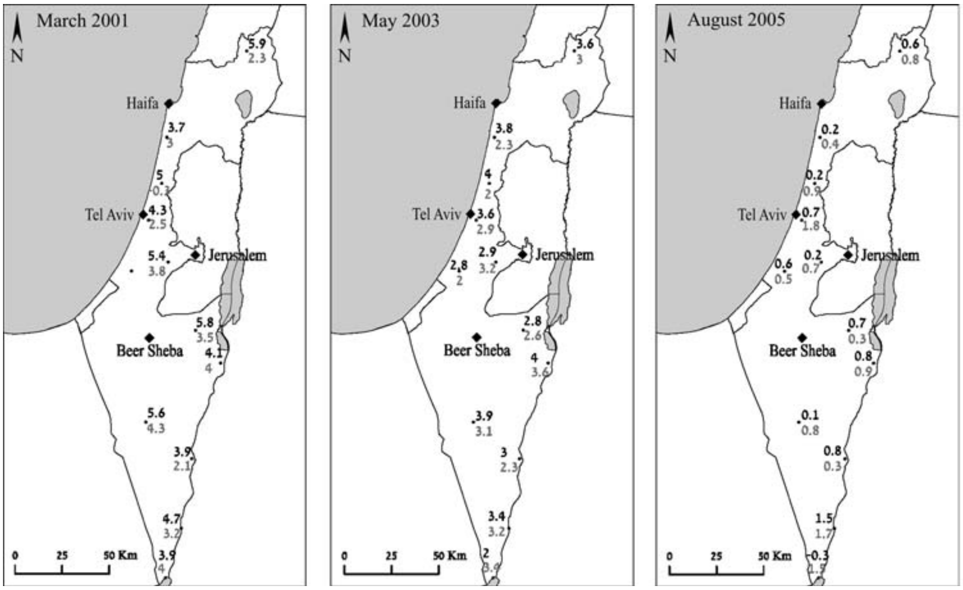


**Figure 2.** Temperature anomalies in selected months (March 2001, April 2003, and August 2005). The black value refers to the monthly maximum temperature, and the gray value represents the monthly minimum temperature.

anomaly is apparent in the three examples in Figure 2, which illustrates the positive anomalies of the mean monthly temperatures (maximum and minimum) from the perennial averages (maximum and minimum). This refers to the end of winter (March 2001), spring (May 2003), and mid-summer (August 2005). In 4 out of the 5 months of March (2001–2005), an increase in the maximum temperature was found. Most cases showed an anomaly of more than 3°C (an extreme anomaly of more than 5.5°C was detected in March 2001). In the spring (May), the highest anomaly was detected in 2003, with more than 3°C above the perennial averages for both minimum and maximum temperatures. In four out of five summers, positive anomalies were detected in August with 0.5°–1.5°C above the minimum and maximum averages.

## Seasonal Rainfall Contribution

The relative contribution of seasonal rainfall (winter and spring) to the seasonal averages was calculated for the years 2001–2005. Precipitation amounts, as well as rainfall distribution, did not show a spatial coherence along the study period. For example, while rainfall amount in winter 2000–2001 was below average, winter 2002–2003 was very rainy (150% of the winter perennial averages) in the central and northern parts of Israel. While spring 2001 was very dry, spring 2003 was extremely rainy.

## Mosquito Hazard Distribution

Analysis of the distribution of mosquito hazard based on its classification demonstrated that most mosquito concentrations were found in three main areas (see the locations in Figs. 1 and 2): a) along the northern seashore, b) within the center of Israel, and c) throughout the southeastern borders between the Dead Sea and the Red Sea. Medium and severe hazards were found along the study period near the most densely populated areas (central and northern coastal areas).

## Linkages between Temperature and Mosquito Population

Figure 3 demonstrates the linkage between daily average air temperatures and mosquito population hazards (levels 1 to 2), categorized over a 2-week period, in northern Israel. It can be seen that medium to severe hazards are already present in the early spring, weeks before the extreme summer heat.

Figure 4 presents a significant positive linkage with a 2-week lag (result of multinomial logistic regression) between the standardized mean daily temperatures and the mosquito hazard levels (medium and severe hazards) for the years 2002–2005 in the Hula Valley (most northerly station in Fig. 2). The same tendency was found during a longer period in the Hadera district (not shown), north of Tel Aviv. In Tel Aviv itself, this tendency was not found. We assume this is due to the authorities' more efficient treatment of the problem in this central metropolitan area.

## Linkages between Temperature and WNF Cases

Results of Spearman correlation calculation between WNF cases (hospital admission dates) and mean daily tempera-

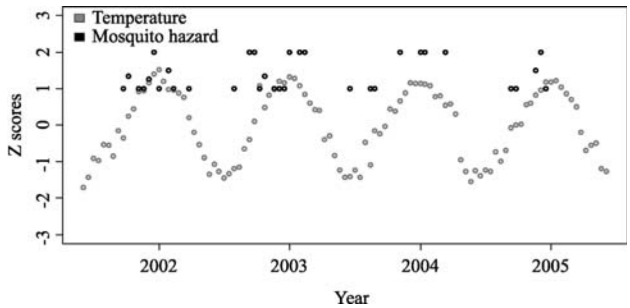


**Figure 3.** Daily average air temperature and mosquito population hazard level (between 1 and 2), categorized into 2-week periods, in the Hula Valley, northern Israel.

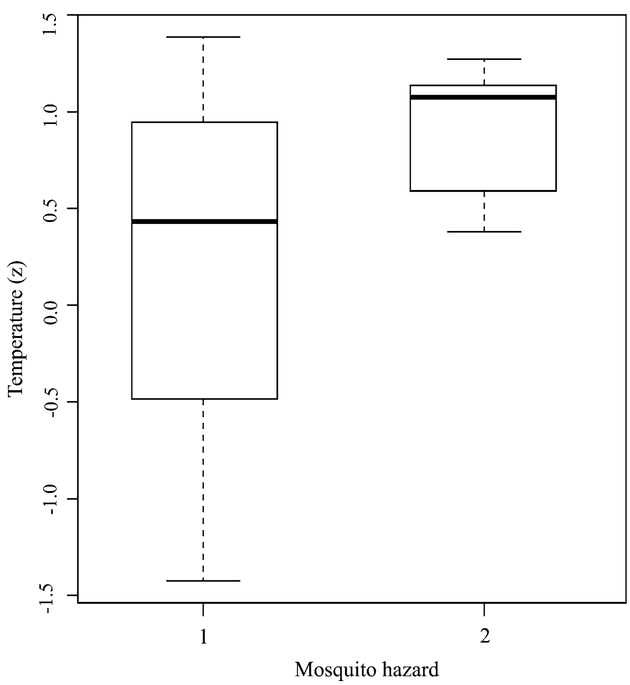


**Figure 4.** Linkage between the standardized mean daily temperatures and the mosquito hazard levels (1 and 2) for the years 2002–2005 in the Hula Valley, with a lag of 2 weeks (results of multinomial logistic regression).

tures for three main districts, throughout the 2001–2005 period, are presented in Table 1. Values were grouped into 2-weekly lags, meaning that Lag 1 = 2 weeks, Lag 2 = 4 weeks, etc. High positive significant correlations ($r \leq 0.62$) were found between temperature increase and a rise in WNF cases in the north during a lag of up to 8 weeks, and for the Hadera district in a lag of up to 6 weeks. Lower correlation was detected for the Tel Aviv area in a lag of 4–6 weeks ($r \leq 0.31$).

**Table 1.** Results of Spearman Correlation Calculation between WNF Cases in Humans (Hospital Admission Dates) and Mean Daily Temperatures, along the Period 2001–2005 in Three Main Districts

| | Spearman Ro | *P* value |
|---|---|---|
| North | | |
| LAG | 0.56 | 0.00 |
| LAG1 | 0.62 | 0.00 |
| LAG2 | 0.62 | 0.00 |
| LAG3 | 0.51 | 0.01 |
| LAG4 | 0.36 | 0.08 |
| Hadera district | | |
| LAG0 | 0.46 | 0.01 |
| LAG1 | 0.59 | 0.00 |
| LAG2 | 0.62 | 0.00 |
| LAG3 | 0.45 | 0.01 |
| LAG4 | 0.24 | 0.18 |
| Tel Aviv | | |
| LAG0 | 0.27 | 0.13 |
| LAG1 | 0.24 | 0.18 |
| LAG2 | 0.30 | 0.09 |
| LAG3 | 0.31 | 0.08 |
| LAG4 | 0.28 | 0.12 |

A similar tendency was found using Pearson cross-correlation calculations between WNF data (admission dates) and minimum/maximum daily temperatures in the Tel Aviv area in 2005 (the year with the highest number of WNF cases). Lag correlation analysis using Z test found significant positive medium linkages ($0.3 \leq r \leq 0.4$). The strongest correlation was found after ~34 days for the daily minimum temperatures and after ~38 days for the daily maximum temperatures.

Significant lag correlations between daily rainfall amounts and WNF cases were not found.

## Discussion

The disease frequency reduced in the years following the WNF outbreak of 2000, when there were 429 cases in humans. This was probably a result of appropriate treatment by health and environmental authorities. This included drying up standing water, the use of pest control systems, and special programs to increase public awareness of the importance of draining standing water sources and using mosquito repellent. However, the risk was still present, with a further increase in morbidity in 2003 and 2005, to 80 and 163 cases, respectively.

Along the study period (2001–2005), most of the WNF cases occurred in the Tel Aviv metropolis, a narrow coastal area, where the heat is very intense due to the combination of high temperatures and a high level of air humidity. This region has a high population density (according to the Israel Central Bureau of Statistics [2006], 6919 humans per sq. km of land lived in the Tel Aviv district in 2005) and suffers from the urban heat island effect, which tends to worsen the local heat conditions (Saaroni et al., 2000). It is interesting to note that Gibbs et al. (2006) also found that the risks associated with WNF outbreaks appear to increase in urban and suburban areas. Human activity supports the mosquito populations by providing food and nesting places, as well as a roosting habitat for native and migrating birds. The local heat inside the cities is another important factor that helps increase mosquito abundance.

The warming tendency during the hot season in Israel over recent years (Saaroni et al., 2003; Paz, 2006; Paz et al., 2007) was ongoing during the study period. It was severe at the end of the winter (March), in spring (May), and less severe in mid-summer (August). During the outbreak of 2000, the disease appeared, on average, at a lag of 3–9 weeks (strongest correlation was found at a lag of 7 weeks) (Paz, 2006). Here again, the positive lag correlations between air temperature and mosquito hazard level/WNF cases indicate the significance of temperature increase at the beginning of the hot season, weeks before the disease's main appearance at mid-summer. This supports Paz (2006), who noted that an early extreme rise in temperature in the hot season could be a good indicator of increased vector populations.

The increase in mosquito hazards and in WNF cases in 2003 (Fig. 1) could be related to the extreme heat at the beginning of the spring, but also to the unusual increase in rainfall amount in the previous winter and spring (see the Results section, paragraph 3). It is reasonable to assume that these precipitations could enlarge the standing water recourses at the beginning of the hot season. This supposition is different from previous studies (Epstein and Defilippo, 2001; Epstein, 2005; Tibbetts, 2007), which noted that WNF increases after an extreme dry period, since standing water pools become richer in organic materials. We claim that these conclusions fit regions with larger amounts of precipitation throughout a longer rainy season. However, in a Mediterranean climate type (which also characterizes areas located as far from the Mediterranean Basin as California, Cape Town in South Africa, central Chile, and southwestern Australia), when the rainfall regime consists of a long dry summer without any rainfall, the usual conditions are severe drought and dry pools during the summer. Therefore, an increase in rainfall amounts in the spring might be an important parameter that expands the mass of water ponds. When *Culex pipiens* population breeds in standing water, wild or urban domestic birds may circulate around the ponds and thus increase interaction with mosquitoes. This insight is similar to the finding of Hubalek and Halouzka (1999), who noted that heavy rains could increase the incidence of WNF in Europe.

Yet, looking at the highest disease distribution in 2005 (Fig. 1), when spring rainfall was below the average in the Tel Aviv metropolis (not shown), we assume that the increase in WNF cases in 2005 could be a result of the severe heat during that summer. July and August were extremely hot, while almost 2°C above the average minimum temperature was noted during the nights in the Tel Aviv metropolis. In light of this, it is worth noting that Paz (2006) indicated that the minimum temperature is the most important climatic factor that encourages the disease's earlier appearance.

It is interesting to compare the morbidity increase during 2003 (rainy spring) and 2005 (severe heat). In 2003, 32% of WNF cases occurred between April and June, when only 6% of cases occurred in the same period in 2005; but in contrast, while 55% of cases occurred after August 1, 2003, 85% of the admissions to hospital occurred after the same date in 2005, probably as a result of the extreme July heat.

Based on the findings in the current research, we recommend that in a Mediterranean climate type, two indicators may encourage the WNF appearance—rainy spring and/or severe heat.

## Conclusions

The current study of WNF in Israel throughout 2001–2005 shows that the disease appearance reflects the population distribution, while the risk tends to escalate around urban areas that are characterized by an urban heat island.

Constant positive anomalies of the minimum and maximum temperatures during the study period appear to have facilitated the mosquito abundance and, consequently, the disease emergence in humans. An important finding is the potential influence of extreme heat in the early spring on the vector population increase and on the disease's appearance weeks later. Awareness of such situations at the very beginning of the spring may help authorities to reduce the disease risk before it becomes a real danger.

Climate models project a continuing temperature increase over the next decades in the Mediterranean basin (IPCC, 2007b). Despite future uncertainty, the warming tendency has to be considered when predicting further WNF outbreaks.

## Acknowledgments

The authors thank the Israel Ministry of Environmental Protection for funding this project. Thanks are also due to Dr. D. Gandacu from the Department of Epidemiology, Israeli Ministry of Health, for his kind help with the WNF database. The authors thank Alon Haluzi and Noga Yoselevich from the Department of Geography and Environmental Studies, University of Haifa, for their help with preparing the final figures.

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