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Climate change and the emergence of *Vibrio vulnificus* disease in Israel ☆

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Abstract

In 1996, a major unexplained outbreak of systemic *Vibrio vulnificus* infection erupted among Israeli fish market workers. The origins of this emergent infectious disease have not been fully understood. A possible link between climate change and disease emergence is being investigated. Meteorological service data from 1981, the earliest detection and reporting of *V. vulnificus* for the time in Israel, to 1998 for two stations located within the main inland fish farm industry were analyzed. The 1996–1998 summers were identified as the hottest ever recorded in Israel in the previous 40 years. Time series of monthly minimum, maximum, and mean temperatures showed significant increase in the summer temperatures along the 18 years. The highest minimum temperature value was recorded in summer 1996. Lag correlation analysis revealed significant correlations between temperature values and hospital admission dates. The eruption appeared 25–30 days after the extreme heat conditions in summer 1996, at a lag of 3 weeks in summer 1997 while the results for 1998 were at a lag of less than a week. Higher significant results were detected for the daily minimum temperatures in summer 1996 compatible with the disease eruption. These findings suggest that high water temperature might have impacted the ecology of our study area and caused the emergence of the disease, as an effect of global climate change.

Keywords: Climate change; Global warming; Emergence; Israel; *Vibrio vulnificus*

1. Introduction

It is well known that greenhouse gasses emission by human activity enhances the natural greenhouse effect, causing global warming. This trend is accompanied by an increase in the frequency of extreme weather events such as heat waves, floods and droughts (e.g. IPCC, 2001; Gartell, 2001). The increase in temperatures has many global and local aspects, of which the impact of climate change on infectious diseases spreading is central (Cook, 1992; Kuhn et al., 2005). It has been suggested that warmer temperatures may allow mosquitoes that transmit diseases such as malaria (Yang and Ferreira, 2000), dengue fever (Jetten and Focks, 1997), and West Nile fever (Paz, 2006) to extend their ranges and increase both their biting rate and their ability to infect humans. The relationship between infections caused by waterborne pathogens and global warming is even more interesting. A rise in sea surface temperature in a given area occurring shortly before an increase in the number of people infected with cholera has been suggested as a possible impact of climate change on disease spreading (Colwell, 1996). Furthermore, reports of marine-related illnesses along the east cost of the United States had increased over the past 25 years in correlation with El Niño events (Harvell et al., 1999).

Vibrio vulnificus, a naturally occurring, free-living inhabitant of estuarine and marine environments throughout the world, residing in high numbers in filter-feeding shellfish (oysters, clams, and mussels), is considered one of the most dangerous waterborne bacterial pathogens with a case-fatality rate that may reach 50% for *V. vulnificus* septicemia (MMWR, 1993). Microbiological studies have shown that the bacterium is highly sensitive to water temperature and salinity, proliferating in areas

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or during months where the water temperature exceeds 18 °C (Kaspar and Tamplin, 1993) which dictates its seasonality and geographic distribution (Lipp and Rose, 1997; Motes et al., 1998). Low to moderate salinities is also associated with the presence *V. vulnificus* (Motes and DePaola, 1996).

The global epidemiology of *V. vulnificus* is of a recent emergence. Since its recognition as pathogenic to humans in 1970s, disease cases have been reported from many parts of the world (Strom and Paranjpye, 2000). In 1996 a major outbreak of severe soft tissue infections and bacteremia erupted in Israel among fish market workers and fish consumers (Bisharat and Raz, 1996). The implicated fish were cultivated in inland brackish fish farms. Despite some reduction in disease burden, the outbreak continued and handling live fresh fish from inland fish farm has become a significant risk, especially for people suffering from diseases affecting their immune system.

The origins of this emergent disease have not been fully understood. Although originally it was thought to have arisen mostly from human behavior and work practices (Bisharat and Raz, 1996) and based on this assumption, new fish-handling procedures were introduced (Bisharat et al., 1999). However, disease continued, although at a lower incidence. Molecular studies showed that the disease outbreak was caused by a previously undescribed biotype of *V. vulnificus*, exhibiting a distinct phenotypic and molecular pattern (Bisharat et al., 1999). Recent molecular genetic analysis have shown that this biotype is a virulent hybrid variant of the species *V. vulnificus* (Bisharat et al., 2005).

Prior to 1996, no cases of human infections due to *V. vulnificus* were reported from Israel, nevertheless, a halophilic vibrio strain sent from Israel to the Centers for Disease Control and Prevention (CDC), USA, in 1981 from a man who developed wound infection after handling fish, was revived and tested in 1998 and proved to be identical to the disease outbreak strain, *V. vulnificus* biotype 3 (Bisharat et al., 1999).

These findings suggest that the pathogen has been circulating, within the underground brackish water reservoirs, since long before the disease outbreak in 1996. In view of the dramatic disease manifestation caused by *V. vulnificus*, characterized by progressive inflammation of soft tissues and by rapidly progressing erythema, cellulitis, and necrosis, it is unlikely that disease recognition was delayed because of underreporting of disease cases. Therefore, the exact causes of the disease emergence are truly intriguing. Given the organism's dependence on temperature, it is reasonable to speculate that changes in the water temperature of the inland fish farms may have altered the levels of *V. vulnificus* populations in the water, consequently increasing the risk to infect humans. Analysis of air temperature variation over the past decades in Israel could add very important insights into the understanding of the possible link between the disease emergence and climate change.

Israel is located at the eastern Mediterranean basin, a region which is highly sensitive to possible climate changes due to its geographical location between three continents and two climatic influential areas: the Atlantic Ocean and the wide landmass of Asia (Milliman et al., 1992). Available scenarios for the Mediterranean basin linked with the global warming show a significant increase in extreme weather events (Palutikof and Wigley, 1996). Recent studies showed that during the last decades of the 20th century the summers in Israel became warmer with an increase in the frequency and the severity of heat waves (Ben-Gai et al., 1999; Saaroni et al., 2003; Paz, 2006).

Based on these observations, the current study aims to re-analyze the *V. vulnificus* disease outbreak erupting in Israel from a new viewpoint: a possible regional impact of the global warming on the eastern Mediterranean basin.

2. Materials and methods

The current study focuses on two regions—Beit-She'an valley and the Sea of Galilee valley (Fig. 1). These two eastern valleys, located at 200 m$\sim$ below sea level, are parts of the long Syrian-African Rift. The area is characterized by 300–400 mm of precipitation in average per a rainy season, with hot and dry summer (monthly mean temperature is around 32 °C in August). The two regions, particularly Beit-She'an valley, are wealthy in aquifers. The combination of water abundance and high evaporation rate (10.3–11.3 mm/day on average in summer), results in salty water (10–25 ppt). Therefore, one of the most important agriculture sectors in the area is saltwater fishponds.

The data and methods used in the current study are:

1. In order to identify possible climatic situations that could explain the disease appearance, weather conditions were analyzed for the summer of 1996 (*V. Vulnificus* infection reported for the first time in Israel, 35 cases), the summer of 1997 (34 cases) and the summer of 1998 (20 cases). Source: Annual Weather Reports for the Years, 1996–1998, Israel Meteorological Service (IMS) reports.
2. Time series of monthly mean, maximum and minimum temperatures were analyzed (source: IMS) for May–October of 1981–1998 in two representative stations: Zemach (32°42′N/35°35′E; −200 m) for the Sea of Galilee valley, and Sede-Eliyahu (32°26′N/35°30′E; −190 m) for Beit-She'an valley (Fig. 1). This, in order to detect warming tendency from 1981 (when *V. Vulnificus* appeared in fish ponds in Israel) until the summers of 1996–1998 (when disease erupted).
3. Simple regression was calculated between the mean monthly temperatures and the *Vibrio* infection cases per each month, along the three consecutive years 1996–1998.
4. In order to identify lag relations between warm conditions and the disease appearance, Pearson cross correlations were calculated between dates of hospital admission (N. Bisharat, unpublished data), and daily minimum, maximum, and mean temperatures in the above stations for the same period (source: IMS).

3. Results

Between May 1996 and December 1998, 89 cases of wound infection and bacteremia were identified. Most cases were reported during the summer months of each year (Fig. 2). It is believed that more accurate number of such illnesses was recorded in 1998, were partially due to

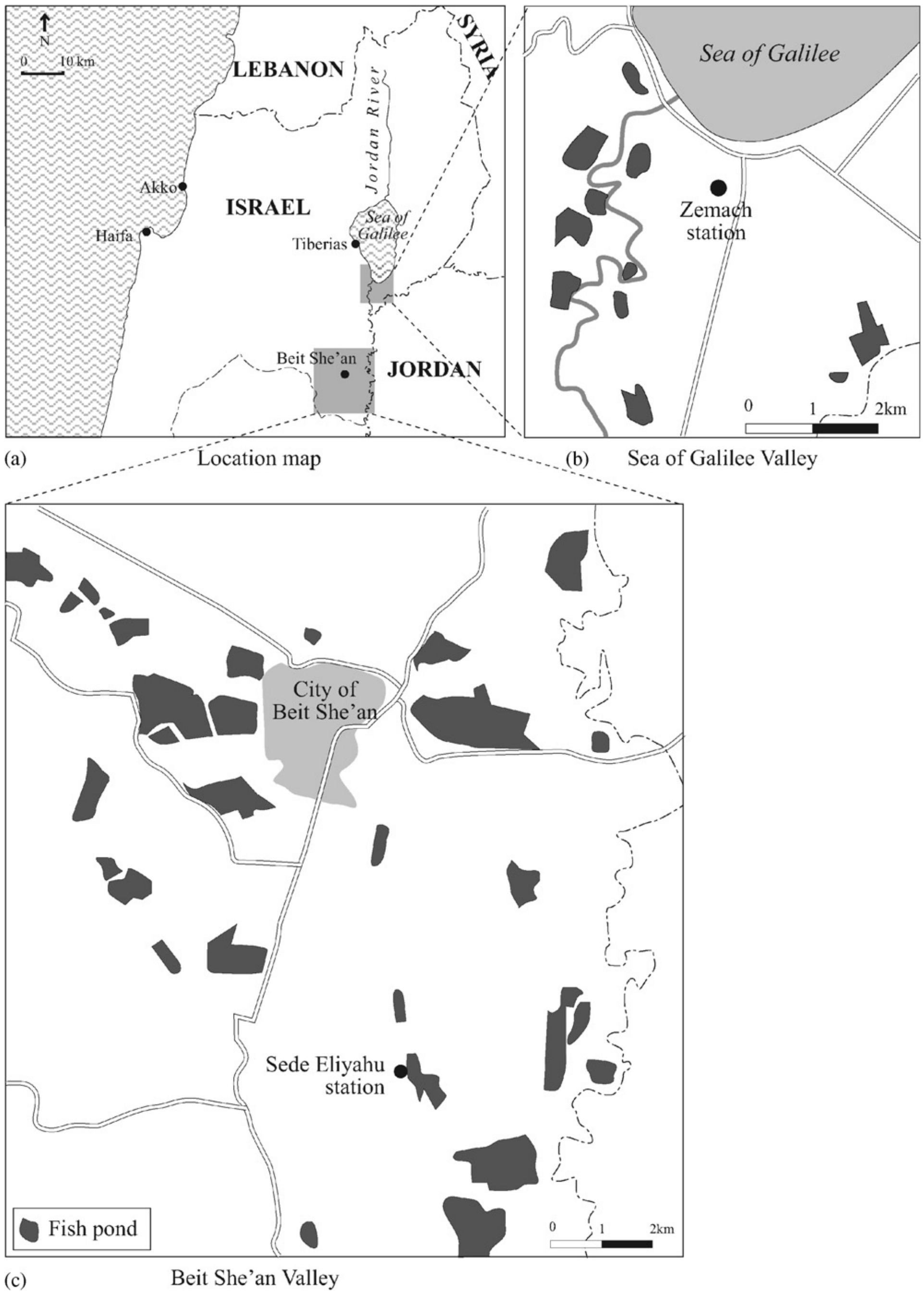

Fig. 1. The Location of Sea of Galilee valley (map b), Beit-She'an valley (map c) and the weather stations.

better awareness among the public and new guidelines established in January of that year for handling and marketing fish, cultivated in inland fish farms (Bisharat et al., 1999).

Simple regression between the mean monthly temperatures at both weather stations and the *V. vulnificus* infection cases per month, show a significant correlation between high temperature and the infection: $r = 0.62$ ($P < 0.0001$). Fig. 2 also presents a linkage between the weather conditions and the disease appearance, with a clear lag time between the highest temperature and the *Vibrio*'s reaction (the lag correlation calculations are discussed in details later).

Examination of the IMS reports that the summer of 1996 was warmer than usual, especially in May, July and August. While two severe heat waves occurred in May (when daily maximum temperatures were above 40 °C in Beit-She'an and Sea of Galilee valleys), July was one of the hottest ever recorded for the last 40 years.

The summer of 1997 was also mostly warmer than usual with several heat waves in May (the maximum temperature was above 40 °C). The heat reached its peak in June 22

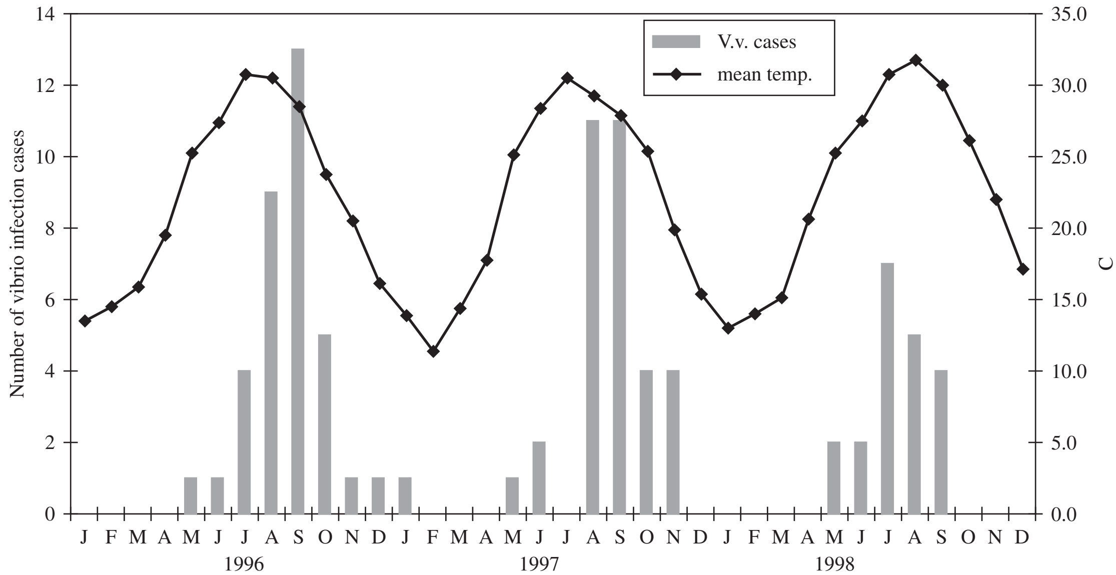

Fig. 2. Mean monthly temperatures at Sede-Eliyahu station and cases of vibrio infection by month of symptom onset (1996–1998).

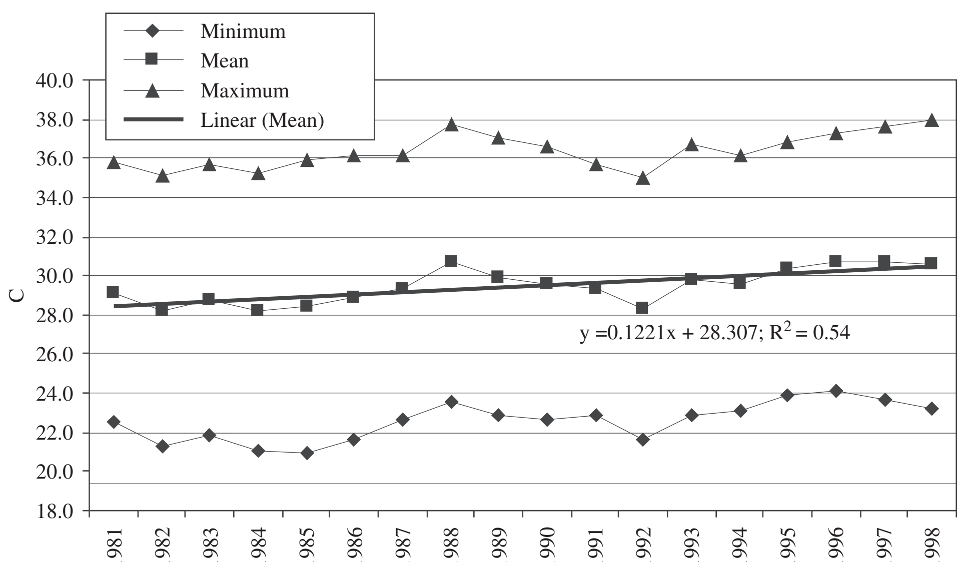

Fig. 3. Minimum, mean and maximum temperatures (°C) at Zemach station in July along the period 1981–1998.

when the maximum temperature was more than 42 °C in Beit-She'an valley. However, temperatures in July and August were below the average.

The period of mid June to mid September 1998 was also extremely hot and in fact summer 1998 was one of the hottest ever recorded in Israel. An extreme heat wave occurred on July 4–5 where day temperature reached 43 °C in Beit-She'an valley. Altogether, the average daily temperature in July and August was one of the highest ever recorded in the previous 40–50 years.

Fig. 3 presents the significant increase in the temperature values along the years 1981–1998 in Zemach station. Interestingly, the highest minimum temperature value was recorded in summer 1996.

Fig. 4 presents the mean daily temperature values at Sede-Eliyahu station together with the dates of disease reports along the period from June 1 to October 31, 1996. The delay between the extreme heat conditions to the disease appearance is seen.

Additionally, lag correlation analysis using Z test found significant positive correlations ($0.3 \leqslant r \leqslant 0.5$; $P < 0.05$) between the mean and minimum temperature values at the two stations, and dates of disease reports, this at a lag of 25–30 days. Despite the ~40 km distance between the two stations, the results for both of them are very similar. The significant results (r-values) for summer 1996 are presented in detail in Table 1. Significant correlations ($0.32 \leqslant r \leqslant 0.49$) were found also for summer 1997 at a lag

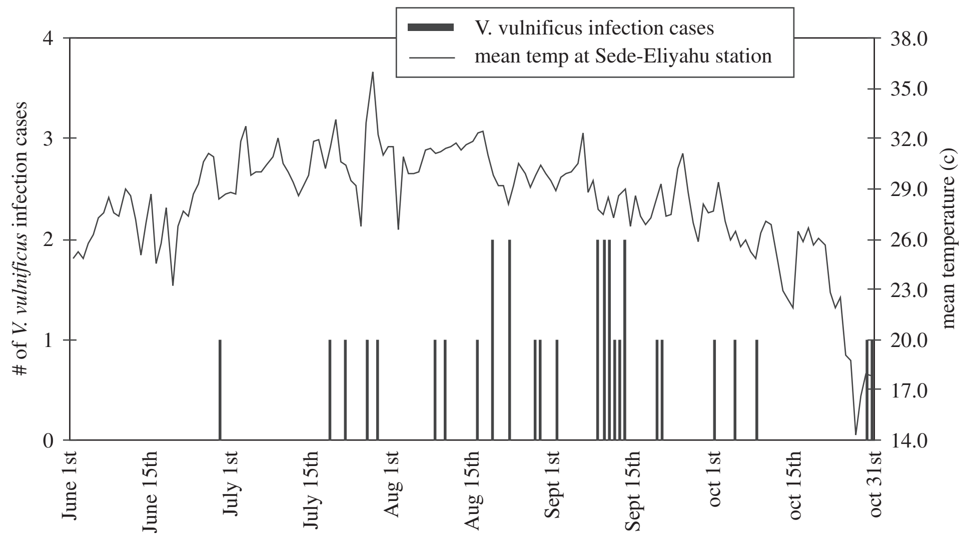

Fig. 4. *V. vulnificus* infection cases and the mean daily temperature values at Sede-Eliyahu station along the period from June 1 to October 31, 1996.

Table 1
Range (in lagged days) of the significant results of lag correlations

Lag correlation time in days	*r*-Values for Sede-Eliyahu		*r*-Values for Zemach	
	Results for mean daily temperature	Results for minimum daily temperature	Results for mean daily temperature	Results for minimum daily temperature
25	0.35	0.50	n.s.	n.s.
26	0.31	0.46	0.48	0.48
27	0.37	0.46	0.48	0.39
28	0.37	0.40	0.47	0.50
29	0.32	0.42	0.40	0.44
30	n.s.	0.35	n.s.	n.s.

(r-values; $P<0.05$) between the temperature values in the climatic stations and *V. vulnificus* admission dates, for the period August 1–September 30, 1996 (n.s. = not significant).

of 3 weeks. However, it is interesting to note that the results for summer 1998 ($0.32 \leqslant r \leqslant 0.48$) were found at a shorter lag time of less than a week.

4. Discussion

Disease vectors have climatic thresholds that govern their abundance and potential for disease transmission. Therefore, an increase in temperatures would cause worldwide net increase in the geographical distribution of vector organisms, with impacts on the timing and severity of infection disease epidemics in many areas of the world (Marsh and Gross, 2001; McMichael, 2003; Kuhn et al., 2005).

Several studies in the last decade have shown that Israel has been affected by the warmest weathers ever on record (e.g. Ben-Gai et al., 1999; Paz, 2006). An analysis by Saaroni et al. (2003) was carried out on temperature records from 1948 to 2002, revealing three distinct warm periods; the warmest began in the mid-1990s. Additionally, the current study found a significant increase in the temperature values along the 18 years from 1981 to 1998. These findings are interestingly well matched with the disease outbreak by the mid-1990s (Bisharat et al., 1999).

The three subsequent summers of 1996, 1997 and 1998 were extremely warm, in some cases hottest than ever recorded, with severe heat waves during days and nights. The occurrence of these extreme weather conditions may be explained as one of the local results of the global warming effects on the eastern Mediterranean basin.

Lag correlation analysis revealed significant correlations between temperature values and hospital admission dates. In summer 1996, the eruption appeared 25–30 days after the extreme heat conditions. Significant correlations were also found for 1997 at a lag of 3 weeks while the results for 1998 were at a lag of less than a week.

Despite the ~40 km distance between Zemach and Sede-Eliyahu, the results were found in both stations at the same lag time. Table 1 presents higher significant results for the daily minimum temperatures, especially for Sede-Eliyahu. It is of interest to note that along the study period (1981–1998), the highest minimum temperature value was recorded in summer 1996 (Fig. 3), compatible with the disease eruption. In view of the extremely high temperatures during both day and night, the minimum temperature becomes an important climatic factor encouraging the earlier appearance of disease, since it increases the lowest climatic threshold of the disease pathogen. The maximum temperature, however, was not identified as a significant factor. Apart of its impact on water temperature, the warming tendency can have a crucial role on the survival curve of the bacterium as it increases the evaporation rate and therefore increases the salinity of the fish ponds waters (Kelly, 1982).

Similar observations regarding disease burden and seasonal changes have been noticed in the Gulf Coast of the USA (Tacket et al., 1984; Gary Hlady and Klontz, 1996) and Southeast Asia (Chuang et al., 1992). Though several factors may have played a role in the disease epidemic, including changes in fish marketing policy (Bisharat and Raz, 1996) and the highly invasive nature of the Israeli clone (Bisharat et al., 2005), its tempting to postulate that regional climate change may have had a major impact on disease emergence. This in fact is largely because the same human-pathogenic clone has been circulating within the fish farms water for at least 17 years without causing any recognized illness and then erupting in 1996.

In summary, constantly rising temperature during the 3-year study period suggest to have facilitated the eruption of *V. vulnificus* disease in Israel during the summer of 1996. We hypothesize that an extreme rise in daily temperatures at the beginning of the summer may predict larger *V. vulnificus* populations in the fish ponds water. Similar observation was made in the occurrence of *V. cholerae* in the Chesapeake Bay related to temperature (Louis et al., 2003). In addition, a small threshold of 5 °C can be major factor to infect human as demonstrated by a recent paper on cholera infection (Huq et al., 2005). However, it calls for further investigation. Climate models project that due to the effects of greenhouse gases and aerosols emissions the global temperature will continue to rise in the next decades. Different models predict an increase of about 1.0–2.0 °C in the Middle East and about 1.5–4.5 °C in southern Europe (IPCC, 1996). Despite the future uncertainty, the warming tendency has to be considered in predicting further outbreaks in Israel and in other places around the world.

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