# What factors determine when epidemics occur in the Mediterranean? Prediction of disease risk through time by climate-driven models of the temporal distribution of outbreaks in Israel

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## Summary

Determination of the temporal relationships between climate and epidemics of *Culicoides*-borne viral disease may lead to control measures and surveillance being implemented earlier and more efficiently. Although Israel has reported few cases of bluetongue (BT) during the recent Mediterranean epidemic, outbreaks have occurred almost annually since the disease was first confirmed there (1950) with severe episodes occurring periodically. The south Mediterranean location and intensive farming of BT-susceptible European sheep breeds make the area ideal for investigation of the effect or role of climatic factors versus other potential host or virus factors in governing the timing of severe BT episodes.

The authors present regression analyses of 20-year time-series of BT outbreaks versus four remotely sensed climatic variables. Low temperatures and high moisture levels (relative to average levels) in the preceding autumn coincident with the seasonal peak of vector abundance and outbreaks had a positive effect on the number of outbreaks the following year. The positive effects of high moisture levels are postulated to increase breeding site availability and refugia for adult *C. imicola* vectors (from desiccation) in autumn whilst low temperatures may increase fecundity, offspring size and survival through adulthood in winter by increasing initial vector population size the following year. The proportion of variance in the annual BT outbreak time series accounted for by climate factors was relatively low (approximately 20%), probably because most BT virus (BTV) circulation occurs silently, due to the circulation of non-virulent BTV strains, combined with the prevalence of relatively resistant local sheep breeds. Thus, the level of BTV transmission is poorly correlated with the rate of outbreak notification.

## Keywords

Bluetongue – Climate – *Culicoides imicola* – Epidemic – Israel – Mediterranean – Remote-sensing – Time-series analysis.

## Introduction

The recent unprecedented epidemic of bluetongue (BT) in the Mediterranean Basin has led to a spate of studies on the spatial distribution of vectors and virus in this region (5, 15, 17, 18, 42). However, studies of the temporal distribution of *Culicoides* and BT have been limited to restricted areas or short time-scales (46, 48).

Climatic factors may influence the temporal distribution of BT outbreaks via their effects on the life-history parameters and breeding sites of *Culicoides* vectors (29), the main Mediterranean vector species being *C. imicola* Kieffer, 1913. In regard to African horse sickness, another *Culicoides*-borne disease, a strong association was noted between the timing of epidemics during the last century and the warm phase of the El Niño/Southern Oscillation (ENSO) in South Africa due to the combination of rainfall and drought brought by this phase (4). In both Israel and Cyprus, severe BT outbreaks were preceded by higher than average rainfall in winter or autumn (33, 34, 39, 40) that increases the availability of suitable breeding sites for *C. imicola*. This species breeds in rich mixtures of organic matter and wet soil (without surface water) (8).

Other potential factors that could influence the temporal distribution of BT outbreaks include the occurrence of viral incursion in surrounding countries (Fig. 1), the introduction of new viral strains (20) and the variation in presence of susceptible hosts (and levels of herd immunity). Sellers (37) was the first to note the simultaneous appearance of BT outbreaks in southern Mediterranean countries in 1943 to 1944 (Cyprus, Turkey, Syria and Israel), in 1950 to 1951 (Cyprus and Israel) and in 1964 to 1965 (Cyprus, Israel and Egypt) (Fig. 1). This observation has since been developed further by Hassan (24) and Taylor (44, 45) for later outbreaks. The rate at which outbreaks occur or are notified may depend on the turnover, annual vaccination coverage (40) or importation of susceptible sheep breeds. In the 1960s, outbreaks were preceded in both Israel (39) and Egypt (1, 22) by the importation of German Merino breeds, to which cases were largely restricted, whilst local African sheep breeds (such as Awassi) were relatively unaffected (26).

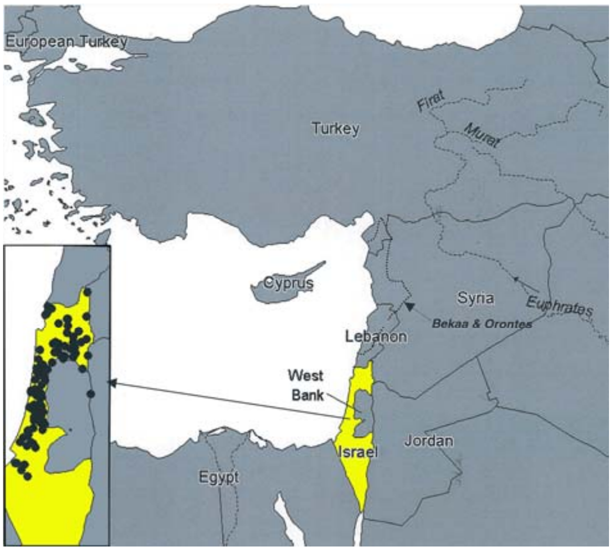


Figure 1
Countries of the south-eastern Mediterranean Basin, showing the location of bluetongue outbreaks in recent severe episodes in Israel, 1987, 1993, 1994, 1996 (inset)

The authors present an investigation of whether the timing of severe BT outbreaks is attributable to climatic factors in Israel compared to other potential host or virus factors. The authors analyse relationships between a continuous 20-year monthly bluetongue incidence data-set and monthly climatic variables derived from remotely-sensed advanced very high resolution radiometer (AVHRR) data (8 km spatial resolution).

## Material and methods

### Study area

Israel includes areas of relatively moist temperate climate in the north (coastal plains), cool central mountain ranges and an arid desert area in the south (Negev). The annual climate can be divided into a rainy season between October and April (peak rainfall and minimum temperatures are December to February) and a dry season from May to August (usually to October). The livestock population of Israel usually comprises approximately 320 000 bovines, 100 000 goats and 300 000 ovines. In the past, approximately 25% of the sheep population were exotic breeds and their crosses (40). In the Jewish sector, from which much of the BT outbreak data is derived, the sheep population is currently made up of 50 000 Awassi, 20 000 Merino and 120 000 Assaf (East Friesian × Awassi). Since 1964, the latter are vaccinated annually using a polyvalent vaccine from the Onderstepoort Veterinary Institute (containing live attenuated BTV types 2, 4, 6, 10 and 16) changing in 1974 to a quadrivalent vaccine (types 2, 4, 6 and 10). The spatial distribution of 116 villages affected by BT during recent severe outbreaks is shown in the inset of Figure 1 (M. Van Ham, unpublished data). This village distribution (point data) was overlaid on the 8 km × 8 km pixels of Israel to identify pixels within 4 km of an outbreak (outbreak pixels).

### Incidence data, vector and remotely-sensed climatic time-series data and data analysis

Sources, time period covered and form of entomological, epidemiological and climate time series data available for analyses are summarised in Table I. The environmental significance of the remotely-sensed climate variables is as follows: normalised difference vegetation index (NDVI) specifically measures chlorophyll abundance and light absorption, but is correlated with soil moisture, rainfall and vegetation biomass, coverage and productivity (16). Middle infa-red reflectance (MIR) is correlated with the water content, surface temperature and structure of vegetation canopies (6). Land surface temperature (LST) is a general index of the apparent environmental surface temperature (whether soil or vegetation) and air temperature

Table I
Sources, period and form of entomological, epidemiological and climate time-series data available for analysis

| Data type | Period and continuity | Variable form | Source |
|---|---|---|---|
| Bluetongue incidence | 1968-2002 | Monthly numbers of BT outbreaks in sheep flocks in Israel<br>Annual total of outbreaks<br>Annual duration of the outbreaks (months)<br>Proportion of annual total of outbreaks contained in each month | Israeli Veterinary Services |
| Vector numbers | 1992-1997<br>2001-2002<br>July-December | Daily maximum trap catch of *C. imicola* across all traps<br>Monthly index of abundance i.e. monthly average across daily maximum trap catches<br>Mean of proportion of annual vector population contained in each month | Du Toit light-trap collections from Beit Dagan (32º05′N, 34º50′E)<br>(9, 11, 12) |
| Climate (remotely-sensed data) | 1981-1994<br>1985-1999 | Monthly middle infra-red reflectance (MIR)<br>Monthly land surface temperature (LST)<br>Monthly air temperature (TAIR)<br>Monthly were normalised difference vegetation index (NDVI)<br>All variables were averaged across outbreak pixels | Pathfinder advanced very high resolution radiometer (AVHRR) imagery at 8 by 8 km resolution (36) |
| Climate (weather station data) | | Monthly minimum and maximum temperature (Jan-Dec)<br>Average daily minimum and maximum temperatures (Jan-Dec)<br>Monthly rainfall quantities (Sept-May) | Kefar Blum (33º09′N, 35º38′E) weather station |

(TAIR) is an estimate of the air temperature a few metres above the land surface (21).

## Data analysis

Strong seasonal variation was removed from the monthly climate time series by seasonal decomposition (19) in MINITAB® release 12.21. An additive model of the type $X_t = mt + S_t + \varepsilon_t$ was used for seasonal decomposition (where $mt$ is the deseasonalised mean level at time $t$, $S_t$ is the seasonal effect at time $t$, and $\varepsilon_t$ is the random error), to make the seasonal effect constant from year to year. Since seasonal decomposition was unsuccessful for the monthly BT outbreak time series, analysis was based on raw monthly and annual totals of BT outbreaks.

## Relationship between outbreaks and climate variables

Cross-correlation functions (CCF) were calculated between the monthly totals of BT outbreaks and the deseasonalised climate variables (one CCF was calculated from 1981-1994 and one from 1995-1999).

On an annual time-scale, a linear regression was calculated between the annual total of BT outbreaks (log-transformed), the year (to consider the linear temporal trend) and 40 independent climatic variables. These were, for each of the deseasonalised TAIR, NDVI, LST and MIR: annual mean, annual minimum, annual maximum, annual amplitude, mean of the variable across months within each quarter of the same year and within the last two quarters of the previous year (the quarters being January to March, April to June, July to September and October to December). Variables significant in univariate regressions were then included in a global model and the best one (or two) variable model was chosen by 'best subsets' regression. This process was repeated with the duration of outbreaks as the dependent variable. CCFs were calculated between deseasonalised satellite-derived variables and weather station-derived variables for Kefar Blum. A Spearman's rank correlation was calculated between monthly rainfall amounts (only available for September to May for each year) and satellite-derived variables.

# Results

## Temporal patterns in an outbreak, vector and climatic time series

A total of 386 outbreaks of BT were recorded between 1968 and 2001 in Israel. They occurred almost annually (Fig. 2) (range: 0 to 60 outbreaks a year) and only 6 of 34 years (18%) had no outbreaks. However, 50% of years had five outbreaks or fewer. More than 20 outbreaks occurred in 1969, 1975, 1987, 1988, 1991 and 1994 (18% of years). The annual duration of the outbreaks ranged from one to six months (mean duration ± s.e = 3.14 ± 2.84) and there was a significant positive correlation between the annual total of outbreaks and their duration (Spearman's rank correlation $r_s = 0.76$, $p<0.001$, $n = 28$).

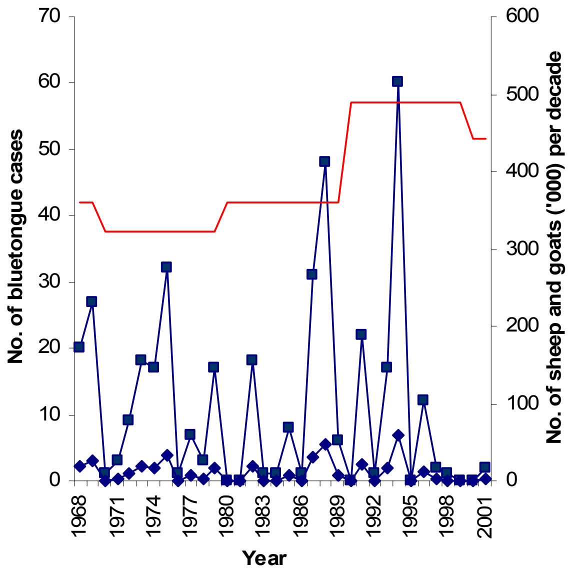


Figure 2
Annual time-series of bluetongue cases and livestock numbers (1 000s per decade)

Outbreaks only occurred between July and January in the year but were concentrated in October and November when 71% of all outbreaks were detected with 21% detected in August and September (Fig. 3). The seasonal distribution of outbreaks is mirrored by that of the vector *C. imicola* populations.

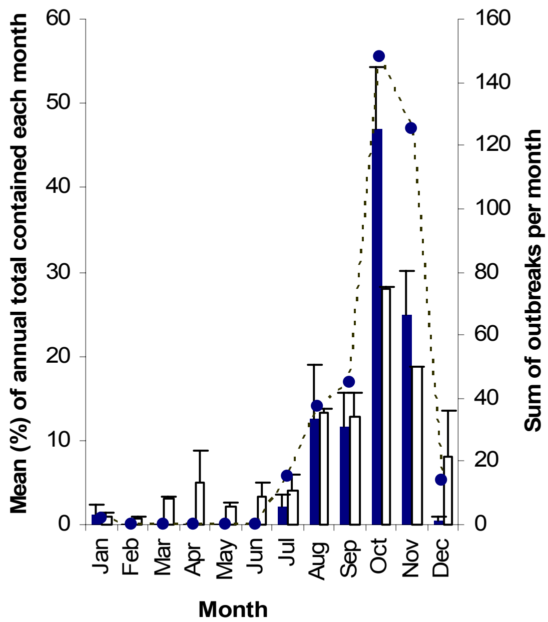


Figure 3
Seasonal distribution of bluetongue outbreaks and vector *Culicoides imicola* populations
Closed bars: mean (± s.e.) proportion of the annual total of outbreaks contained in each month over six years with >20 outbreaks
Open bars: mean (± s.e.) proportion of the annual total of *C. imicola* contained in each month in 2001 and 2001 at Beit Dagan
Closed circles: sum of outbreaks contained in each month over all years (1968-2001)

## Relationship between outbreaks and climatic variables

Between 1981 and 1994, monthly BT outbreak numbers were negatively correlated with MIR ($r = -0.26$), TAIR ($r = -0.26$) and LST ($r = -0.28$) at a lag of 1 month. Between 1995 and 1999, monthly BT outbreak numbers were negatively correlated with MIR ($r = -0.13$), TAIR ($r = -0.35$) and LST ($r = -0.23$) at a lag of five months and positively correlated with NDVI in the same month ($r = -0.31$) and at a lag of four months ($r = -0.26$). These results suggest that outbreaks are less likely in a month when preceded by periods of high temperature (indicated by high LST, MIR or TAIR) one to five months earlier. Outbreaks are more likely to occur when moist conditions prevail (indicated by high NDVI) in a particular month or up to four months previously.

There was no significant relationship between the annual total of outbreaks and year ($F_{1, 17} = 0.05$, $p = 0.82$, adjusted $R^2 = 0.0$) or duration of outbreaks and year ($F_{1, 17} = 0.03$, $p = 0.88$, adjusted $R^2 = 0.0$) indicating that there was no linear temporal trend. The annual total of outbreaks was negatively related to mean LST (equation; y = 28.8-0.091*mean LST; $F_{1, 17} = 4.7$, $p = 0.047$, adjusted $R^2 = 18.7$) and mean MIR (equation; y = 24.2-0.076*mean MIR: $F_{1, 17} = 5.6$, $p = 0.032$, adjusted $R^2 = 22.2$) in the last quarter of the previous year (October to December). It was unrelated to all other independent variables. A regression model including both variables did not sufficiently increase the amount of variance explained by the predictor variables to justify the inclusion of LST (equation; y = 22.7-0.091*mean MIR + 0.02*mean LST: $F_{1, 17} = 2.6$, $p = 0.109$, adjusted $R^2 = 16.8$). Thus, mean MIR in the last quarter of the previous year was the predictor of the annual total number of outbreaks (i.e. the most parsimonious model). Figure 4 shows observed time series of outbreaks compared to that derived from the fitted values from this relationship. The observation for the 1994 outbreak year had a large influence in these regressions (equation omitting 1994; y = 20.0-0.062 mean MIR: $F_{1, 15} = 2.1$, $p = 0.169$, adjusted $R^2 = 6.5$).

The duration of outbreaks was negatively related to mean LST in the last quarter of the previous year (equation; y = 93.4-0.296*mean LST; $F_{1, 15} = 6.5$, $p = 0.023$, adjusted $R^2 = 25.4$) and 1994 again had a large influence on this relationship (equation omitting 1994; y = 88.3-0.280 mean LST: $F_{1, 14} = 3.1$, $p = 0.10$, adjusted $R^2 = 12.3$).

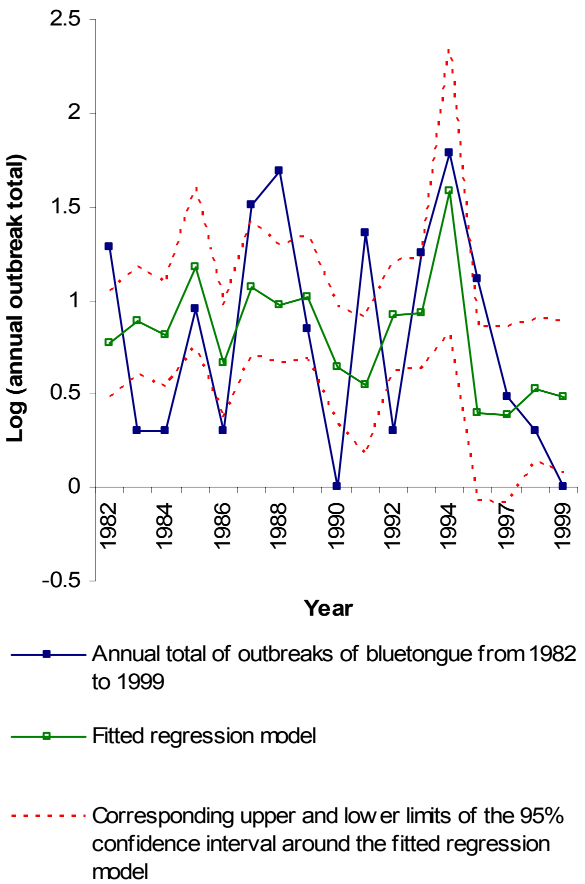


Figure 4
Results of the regression model
(y = 24.2-0.076*mean MIR)

## Relationship between satellite-derived and weather station derived climate variables for Kefar Blum

Monthly minimum temperatures were uncorrelated with satellite-derived variables whist monthly maximum temperatures were positively correlated with TAIR ($r$ = 0.32), LST ($r$ = 0.26) and MIR ($r$ = 0.30) in the same month. Since three images are maximum-composited to produce the monthly satellite variables, one would not expect them to be correlated with monthly minimum temperatures. Average daily minimum temperatures were negatively correlated with the NDVI in the same month (r = –0.26) and positively correlated with MIR ($r$ = 0.29) and LST ($r$ = 0.28) in the same month. Average daily maximum temperatures were negatively correlated with the NDVI one month later (r = –0.24) and positively correlated with TAIR ($r$ = 0.39), MIR ($r$ = 0.33) and LST ($r$ = 0.36) in the same month. Monthly rainfall amount was correlated with MIR (Spearman's rank $r_s$ = –0.17, $p$ = 0.03, $n$ = 162) and LST (Spearman's rank $r_s$ = –0.18, $p$ = 0.02, $n$ = 162) in the same month.

## Discussion

Bluetongue outbreaks are significantly related to satellite-derived climate variables in Israel with some degree of delay. This suggests potential for a climate-based early warning system for BT, contingent on further detailed analyses of these relationships.

On a monthly basis, BT outbreak numbers decreased with high temperatures (TAIR and LST) and MIR in the preceding months (one to five months before) and increased with high NDVI in the same and preceding months (four months before). On an annual basis, total outbreaks decreased with high MIR in the quarter at the end of the previous year (October to December). The duration of outbreaks the following year was reduced by warm temperatures (LST) in the same period. Thus low temperatures (indicated by low LST, TAIR and MIR) and high moisture levels (indicated by low MIR and high NDVI) have a positive effect on the number of outbreaks in Israel. Conditions in the preceding year, between October and December, appeared to be more important than spring or early summer conditions in the same year.

Previous spatial satellite-driven models of abundance of the vector *C. imicola* have found positive effects of high moisture levels, i.e. high or early peaks in NDVI (2, 3, 5, 42). Short-term temporal studies found increases in this species abundance following rainfall (31, 46). In addition, severe BT outbreaks were observed to be preceded by higher than average rainfall in autumn or winter (33, 34, 39, 40).

Due to its location in the southern Mediterranean, Israel has a mixture of warm, temperate and arid desert climates. Temperature conditions will generally be far from the lower limits required for development of *C. imicola* vectors whilst moist conditions may generally be close to the lower limits of the requirements for this species. This is consistent with the restriction of BT outbreaks to northern lowland areas and river valleys in Israel (that probably broadly reflect the distribution of *C. imicola* abundance). The number of outbreaks the following year may depend on the initial size of the vector population after the winter period and the transmission intensity both during the previous autumn peak of vector and virus populations and over winter. High moisture levels during the peak of vector abundance will increase the availability and quality of breeding sites (wet soil and organic matter) (8) and provide refugia where adults can resist desiccation (30). Low temperatures during autumn and winter may have positive effects on fecundity, offspring size (27) and survival through adulthood (25, 47) and so increase initial adult population size the following year. These mechanisms may produce the positive annual relationship between outbreaks and low temperature and high moisture in late autumn and winter observed in Israel. The opposite relationship may arise further north in Europe, at the northern range limit of *C. imicola*. Here, proximity to the lower temperature limit for development within moist climates produces positive effects of high temperature and relatively dry summer conditions on *C. imicola* abundance (32, 35).

Braverman *et al.* (14) point out that no BT outbreaks occur after very cold winters such as that of 1991-1992. Indeed, for 1992, our satellite-driven model over-estimates the likelihood of outbreaks (Fig. 4). Since satellite variables are maximum-composited, extreme climatic minima may not be represented in their time-series. Thus the effect of very low temperatures, for example, on numbers of outbreaks may not be testable.

The proportion of variance in the epidemiological time-series accounted for by climate factors is relatively low (approximately 20%) (Fig. 4). The rate at which BT outbreaks are notified is unlikely to be proportional to the actual level of virus circulation for two reasons. Firstly, a large proportion of the sheep population has consisted of relatively resistant breeds in the past (40) in which BTV circulation occurs without any detectable clinical signs. The sheep population currently consists mainly of Assaf in which less severe BT cases (relative to those in Merinos) are usually observed (41). Thus, long-term variation in the importation, movements and vaccination of such sheep within the country will have affected the rate of BT outbreak notification. In addition, there is evidence of high rates of seroconversion to BTV in sentinel cattle in several years without high numbers of outbreaks, suggesting that many strains of BTV are non-virulent (41). For example, in 1983 and 1984, where the satellite-driven model over-estimates the number of BT outbreaks, there was a high rate of seroconversion to serotypes 2, 4 and 6 across Israel. In the absence of annual, standardised, sentinel surveillance data, a strong relationship between climate and virus circulation is not easily detectable with such a data set. Other factors, such as the occurrence of a viral incursion from surrounding countries, may affect the temporal distribution of outbreaks. Most authors in surrounding countries assert that BTV circulates continually undetected in resistant livestock (23, 37, 44) such that sources of viral incursion should frequently be available. However, only five (1, 2, 4, 13, 16) of the ten different BTV serotypes recorded in adjacent countries (1, 2, 3, 4, 6, 9, 11, 13, 14, 16) have been detected in Israel (39). This, together with the considerable temporal variation in serotype prevalence in Israel, suggests that occurrence of incursions from surrounding countries, permitted probably by wind dispersal of infected midges, plays some role in the dynamics of BTV in Israel. As such, temporal variation in wind speed and direction should be considered in future models (7, 10, 13, 28, 33, 38, 44), although these factors are also inherently difficult to quantify. An examination of BT case data from the current epidemic in relation to a range of moderate resolution imaging spectroradiometer (MODIS) imagery (43) at shorter time-scales may reveal stronger relationships between climate and the timing of outbreaks that are more useful for outbreak prediction.

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