Boutonneuse Fever and Climate Variability

RITA DE SOUSA, TERESA LUZ, PAULO PARREIRA, MARGARIDA SANTOS-SILVA, AND FATIMA BACELLAR

CEVDI, National Institute of Health Dr. Ricardo Jorge, Águas de Moura, Portugal

ABSTRACT: Researchers have long appreciated the role of climate in vector-borne diseases, including the resurgence of boutonneuse fever (BF). Portugal usually is classified as having temperate Mediterranean climate. In this new century, in analyzing the data from the Meteorology Institute, this pattern has changed and an accentuated variability in climate is being observed. BF (*febre escaro nodular*) is endemic and high season is from late spring and summer. The brown dog tick *Rhipicephalus sanguineus.* is the vector and reservoir of *Rickettsia conorii complex* strains: *R. conorii* Malish and Israeli spotted fever strain. To assess the influence of climate change in BF seasonality our aim was to compare the human sera samples received at CEVDI–INSA for laboratory diagnosis of MSF for 5 months per year from October to February, ("off-season") from 2000 to 2005. Of 1,299 sera samples in persons with suspected clinical diagnosis of MSF, 45 (3.4%) were considered positive cases and the number of positive cases has doubled in the last 2 years. BF epidemiology clearly appears to be associated with climate change, especially with low precipitation values. Physicians should be aware of increasing off-season BF cases.

KEYWORDS: boutonneuse fever; *Rhipicephalus sanguineus* ticks; climate variability; Portugal

INTRODUCTION

In 1996 the Intergovernmental Panel on Climate Change from the United Nations stated that "climate change is likely to have wide-ranging and mostly adverse impacts on human health, with significant loss of life exacerbating and accelerating the tempo of contemporary infectious disease emergence, particularly for those diseases transmitted by an intermediate host, or vector."[1]

Address for correspondence: Fátima Bacellar, Centro de Estudos de Vectores e Doenças Infecciosas, Instituto Nacional de Saúde Dr. Ricardo Jorge, Avenida da Liberdade 5, 2965-575 Águas de Moura, Portugal. Voice: +351-265-912222; fax: +351-265-912568;+351-265-912155.
e-mail: fatima.bacellar@insa.min-saude.pt

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Over the last decades several vector-borne diseases have emerged, expanded, or reemerged, for example, Lyme borreliosis, anaplasmosis/ehrlichiosis, malaria, and dengue. The resurgence of boutonneuse fever (BF) in Spain and Italy were examples of climate-related changes associated with the prevalence or distribution of pathogens and their vectors.[2]

The climate in Portugal is classified as temperate Mediterranean type. The normal value range (1961–1990) for average annual air temperature is 9°C to 23°C and precipitation varies from 600 mm in the lowlands south of River Tejo to 1500 mm in the mountainous north.[3]

In Portugal BF (Febre escaro nodular- ICD10: A77.1) is endemic and the most reported tick-borne disease having an annual incidence of $8.9/10^5$ inhabitants (1989–2003).[4]

Rickettsia conorii conorii and *Rickettsia conorii israeli* are the BF agents and their vector and reservoir is the brown dog tick.

The tick species *Rhipicephalus sanguineus* is adapted to higher temperatures with humidity being the limiting survival factor.[5] In the laboratory it can survive in extreme conditions (8°C–40°C/45% humidity) and its life cycle can be completed in less than 10 weeks.[6] *R. sanguineus* is generally an exophilic three-host tick, but usually, in domestic environments, the larvae, nymphs, and adults may be found on dogs all over the year. In the last few years variability in temperature and rainfall patterns is being observed, mainly generating warmer and drier winters.[7] The abundance and seasonal dynamics of ticks are influenced by climatic conditions and although the risk of transmission of rickettsiae is dependent on several parameters, such as prevalence of rickettsia-infected ticks and affinity of specific ticks for humans, climatic changes have influence on the abundance and tick activity and consequently on the incidence of BF. The aim of this work was to discern whether the known seasonality of BF is being changed by the influence of climate variability in Portugal.

MATERIALS AND METHODS

Meteorological Data Collection

Data on air temperature and precipitation were collected at the Institute of Meteorology (IM)<http://www.meteo.pt/>. Air temperature values from October to February during the 2000–2005 period are presented as average values combining data from all meteorological stations. Data on precipitation are presented for the October 2003 to February 2004 period individually for each meteorological station. This period was chosen as a representation of the differences observed from normal values.

Sample

One thousand, two hundred, and ninety-nine human samples of clinically suspected cases of BF were received at CEVDI for 5 months per year (October to February) during 2000–2005.

Case Definition

A patient seroconversion in two samples collected from October to February proved an "off-season" BF case, as well the positive isolation of rickettsiae from total blood. A positive case was defined also by a single sample with IgM $>$ 1:32 in combination with IgG $>$ 1:128 dilutions.[5]

Laboratory Tests

Immunofluorescence assay (IFA) was done as described elsewhere using an in-house *R. conorii* conorii antigen. The cutoff used in CEVDI is a titer of $>$128 for IgG and $>$32 for IgM. Suspected cases were considered with titers of IgM $=$ 32 and IgG $=$ 64 and a second sample was solicited. Isolation procedure was as described by Marrero and Raoult in 1989.[8] The isolates were identified by PCR and sequencing with *gtlA* and *rOmpA* primers pairs was described by Regnery *et al*. in 1991.[9]

RESULTS

Meteorological Data

The data obtained at IM show that an overall warmer and drier climate over the 19th and 20th centuries was observed in mainland Portugal (FIG. 1). From 2000 to 2003 the average annual air temperature was slightly above the average normal values (1969–1990). Monthly analysis from October 2003 to February 2004 showed that at the end of winter and early spring temperatures rose about 12°C over the normal mean values, but average minimum and maximum air temperatures were lower, without precipitation. Summer was rainy by contrast. In the period from October 2004 to February 2005 winter began with the highest temperatures ever registered, which were maintained until January 2005. Then the average daily minimum air temperature dropped to unusually negative values and the maximum air temperature did not exceed 15°C all over the territory. There was no rain from November to February. The average data are shown in FIGURE 2. The annual precipitation oscillated from the highest values in 2000–2001, higher than the normal values (the double in the inner northeast), to lower values in 2001–2002, peaking again in 2002–2003 (FIG. 3).

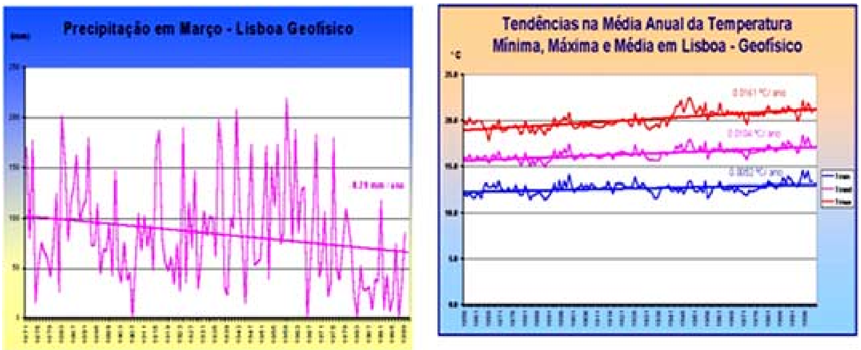

FIGURE 1. Precipitation and air temperature drifts in the 19 and 20th century. Data from IM, March, Lisbon.

Sample Data

Of the 1,299 total samples received in the "off-season" period, 45 (3,46%) were considered positive by case definition (FIG. 4). Of the 45 positive samples 18 (40%) were in males, of whom 58% were in the 60–65 year age group. All

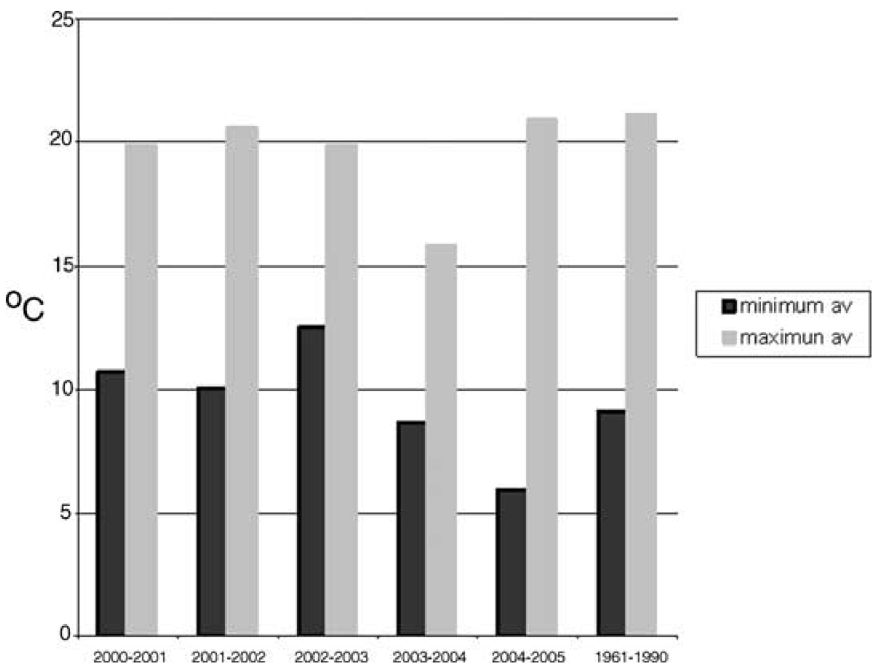

FIGURE 2. Total minimum and maximum air temperature average (°C) in Portugal (October 2000 to February 2005).

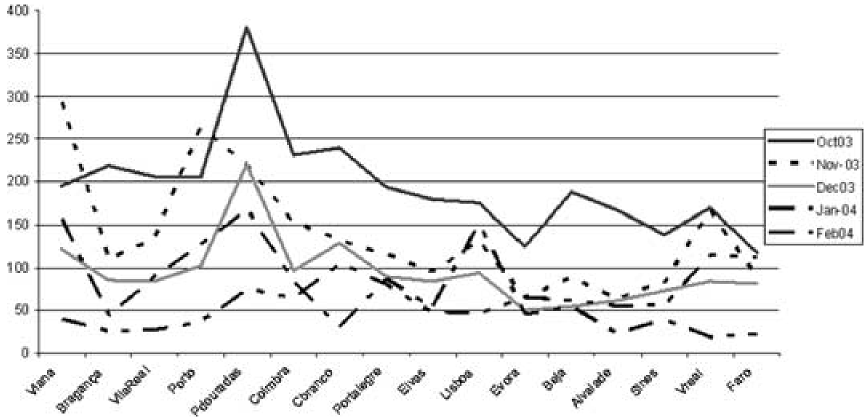

FIGURE 3. Average precipitation (mm) from the northern to southern regions of Portugal (October 2003 to February 2004).

patients were hospitalized, four of whom were admitted to the intensive care unit. In the case report forms the most mentioned symptom was arthralgia (14/45). Two patients had ticks attached. Seroconversion was observed in 51% (23/45) of the positive cases. In the first samples no antibodies were detected or were only at the cut-off level, and the second samples, received 2 to 4 weeks later, had antibody titers of IgM >32 to 1,024 and IgG>128 to 2,048. Half of the positive cases (22/45) had only one sample with IgM over 32 and IgG ranging from 128 to 2,048. The number of positive cases has doubled in the last 2 years. The number of seroconversion increased from one case in October 2000 to February 2001 to 10 cases in October 2003 to February 2004. One isolate was obtained from a total blood sample of a Caucasian male, 68 years old, living in Evora district, hospitalized in the end of January with a respiratory insufficiency syndrome. IFA serology in this sample was considered negative and a second sample was not obtained. The isolate was identified as *R. conorii conorii*.

DISCUSSION

It is a recognized fact that the average global surface temperature has already increased by about 0.6°C. The 1990s were the warmest decade for the northern hemisphere during the previous 1,000 years, and minimum temperatures have been increasing more rapidly than maximum temperatures, generating a concern manifested in several studies supported by the United Nations (United Nations Environment Programme [UNEP]). The precipitation in high latitudes (Northern Hemisphere) is increasing due to that fact, causing winters with shorter snow period.[10] Climate is an important determinant of the spatial and temporal distribution of vectors and pathogens. Therefore, change in

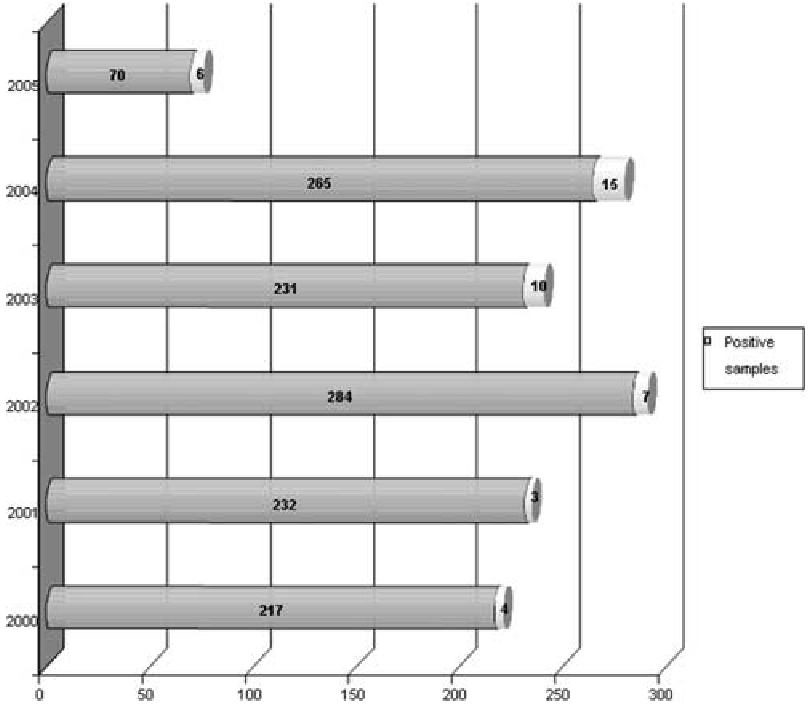

FIGURE 4. CEVDI samples received for BF laboratory diagnosis (October 2000 to February 2005).

climate and climate variability are having a profound impact on the ecology of vector populations, with an expected increase in the incidence and change in the seasonality of vector-borne diseases. On the other hand, maintaining an adaptive seasonality in life cycle is a basic ecological requisite for arthropods, for example, diapause, questing/quiescence behavior are altered physiological states that can be reversed by environmental cues (e.g., photoperiod, humidity level).[11] Ticks are known to be capable of surviving in patch microclimates and to top it off, in laboratory conditions, only changes in humidity appear to have a significant effect on questing nymphs and adults.[12] *R. sanguineus* is documented to be found all over the year in domestic environments, whose conditions of acclimatization allow the life cycle to be completed independently from the natural climate. Generalizing the climate variability observed in Portugal (formerly classified as a temperate Mediterranean type, with cold and heavily rainy winters) during the studied period, that is, warmer air temperature and lower precipitation in winters, one may suppose that even in natural environments *R. sanguineus* survival and broader activity periods are possible.Therefore, as mentioned, it is possible to have three generations in 1 year in the best environmental conditions. The autumn peak of nymphs observed in nature (and indirectly by the BF cases) is probably due to the newly emerged spring-fed larvae added to the nymphs or larvae of the previous year, inducing a multiplying effect in the numbers of questing ticks. Also, the absence of heavy precipitation permits that eggs stay viable, without being washed by rain, and thus hatching occurs in higher numbers also. All data combined, that is, isolation of rickettsiae from one blood sample and seroconversion in all cases presented here, resulted in an observed increase in "off season" BF cases. The serological test does not discriminate among rickettsioses and their results may include infections transmitted by vectors other than *R. sangineus,* such as fleas or other ticks. The results of this study allow the conclusion that BF is not characterized as a seasonal infection anymore and should be considered as the differential diagnosis of a flu-like syndrome in fall and winter. Health personnel and the general public will need to adapt their knowledge and habits to different climatic patterns and to different pathology patterns. Part of the challenge lies in promoting behavior, such as self-protection from tick bites even in winter, in order to prevent tick-borne diseases.

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