Drivers of autochthonous and imported Malaria in Spain and their relationship with meteorological variables

Abstract

Since the early 20th century, the intensity of the transmission of malaria has decreased sharply all over the world, although it is still an infectious disease with a yearly estimate of 228 million cases. Therefore, the aim of this study was to expand the knowledge on the main drivers of malaria in Spain. In the case of autochthonous malaria, these drivers were linked to the socio-economic and hygienic-sanitary conditions, especially in rural areas, due to their proximity to the wetlands required for the reproduction of anophelines. In the case of imported malaria, the main drivers were associated with urban areas, a high population density, and international communication nodes. Another relevant aspect is that the great epidemic episodes of the 20th century were strongly influenced by national war conflict and overcrowding of the healthcare system due to the temporal overlap with the pandemic flu of 1918. Therefore, war conflicts and overlapping with other epidemics or pandemics are considered to be drivers that can—in a temporary manner—exponentially intensify transmission of the disease. Climatic factors did not play a relevant role as drivers of malaria in Spain (at least directly). However, they did influence the seasonality of the disease and, during the epidemic outbreak of 1940-1944, the climate conditions favored or coadjuvated its spread. These results provide further knowledge on the seasonal and interannual variability of malaria, which can help to establish health risk control measures.

Keywords Drivers of malaria, Wetlands, Imported malaria, Autochthonous malaria, Mediterranean climate, Thermal variables

Introduction

Since the early 20th century, the reach and especially the intensity of the transmission of malaria have decreased considerably (Zhao et al. 2016). The estimated number of cases worldwide was 251 million in 2010, 231 million in 2017, and 228 million in 2018, mostly concentrated in Africa (93%; WHO 2019). Therefore, despite the advances of the last decades, malaria is still one of the main health problems, which highlights the need to increase the investment in measures for its eradication and prevention. For instance, although the situation is improving, progress is slow, with 585,000 deaths having occurred in 2010, 416,000 in 2017, and 405,000 in 2018 (WHO 2019). This situation may worsen in endemic countries, since the coronavirus disease (COVID-19) pandemic caused by SARS-CoV-2 poses an additional load to the already overloaded healthcare services, with scarce resources, which fight to control other diseases, such as tuberculosis and HIV (Chanda-Kapata et al. 2020).

In the case of Europe, the indicators related to the socioeconomic improvements (wealth, life expectancy, or degree of urbanization) are strongly associated with the decrease of malaria. At the same time, the indicators that describe the climatic conditions and changes in the uses of soil have shown weaker correlations (Zhao et al. 2016). In the specific case of Spain, autochthonous malaria was declared to have been officially eradicated by the World Health Organization (WHO) in 1964 (Pletsch 1965; Díaz et al. 2005), with the last case of death recorded in 1959 and the last 24 cases of infection in 1961 (Sousa et al. 2009). Although there were cases associated with imported malaria from 1962 (Navarro 2002), a clear progressive increase up to the present time began in the mid-1970s.

The origin of the vectors of the genus *Anopheles*, which transmit the protozoa of the genus *Plasmodium*, which in turn cause malaria, allows different types of malaria to be categorized. From a quantitative perspective, the most frequent types of malaria are indigenous or autochthonous malaria and imported malaria (Sousa et al. 2020). In the case of autochthonous malaria, the disease is acquired from the bite of an infected mosquito in a country where malaria exists. On the other hand, imported malaria refers to patients who acquire the disease in endemic countries and are diagnosed or start showing symptoms in countries where the disease has been eradicated (Díaz-Ballester et al. 2005; López-Vélez and Molina 2005). Currently, the only vector capable of transmitting the disease in a significant manner in Spain is *Anopheles atroparvus*, which exhibits a wide distribution (Díaz et al. 2005; Iriso et al. 2017). However, there is another vector related to malaria in Spain (*Anopheles labranchiae*), which disappeared from southeastern Spain in 1973, but still exists in Northern Africa (Díaz et al. 2005; Blázquez and De Zulueta 1980; Iriso et al. 2017).

An improvement in the socio-economic conditions, and consequently the hygienic-sanitary conditions, is one of the key factors in the eradication of malaria all over the world, since the countries that have managed to eradicate malaria show socio-economic indicators equivalent to those of European countries that have eradicated this disease (Zhao et al. 2016). It is much more complex to establish the role of other factors linked to human activity and, especially, the importance of climatic factors as drivers of the disease. Some studies have analysed the possibility of potential changes in the transmission of malaria due to the effect of climate change on the distribution of anophelines in Europe and the Mediterranean region (Hertig 2019). However, it is important to consider that the influence of temperature on the development of malaria does not seem to be linear (Smith et al. 2014). Therefore, if the variations of temperature are close to the higher limit of the vector and pathogen, the transmission may even tend to decrease. On the contrary, if the variations of daily temperatures are not close to the minimum limit, the transmission may increase, thus also increasing the morbidity of the disease (Smith et al. 2014). Consequently, in order to understand the effect of the climatic variables as drivers of malaria, it is necessary to study the complete historical trends, as well as the historical epidemic outbreaks of the disease. Therefore, several authors have pointed out the importance of better exploring the spatio-temporal drivers of malaria in Europe, improving knowledge on this matter through historical epidemiology (Zhao et al. 2016).

The main objective of this study was to analyse the main drivers of the eradication of autochthonous malaria in Spain through an analysis of the decrease of the disease and its spatial distribution during the 20th century. We explored whether its eradication was a constant and homogeneous process or whether it was affected by epidemic episodes influenced by different drivers. Separately, we also analysed the evolution of imported malaria and its spatial distribution during the 20th century, with the aim of determining whether it was influenced by the same drivers as autochthonous malaria. Once the main non-climate drivers had been analysed, we explored the seasonality of malaria and the interannual influence of the climatic variables. This allowed us to identify whether climatic factors are essential drivers of the intra- and interannual variability of the disease or whether they have little or no relevance.

Material and methods

Since the aim of this study included examining cases of autochthonous and imported malaria, different information sources related to both types of malaria were used. Table 1 presents a general description of the data sources used to obtain the results of the different sections, along with the spatial and temporal scale of the available or used data.

Table 1 around here

Trends of autochthonous malaria during the 20th century

This investigation compiled the available records, from the historical archives, of the number of people infected and deceased by autochthonous malaria in Spain during the 20th century. The recording of the number of deceased people began in 1900, although that of the number of infected people started to be centralized in 1943 (Navarro 2002). The main source of data used was the historical archives of the annual reports of the Spanish Statistics Institute (SSIbase 2020), which have been employed for similar purposes by previous studies on malaria (Rico- Avelló 1950; Fernández-Astasio 2003; Rodríguez-Ocaña et al. 2003; Sousa et al. 2009, 2014) and other infectious diseases that had to be declared (Navarro 2002; Navarro et al. 2012; Chowell et al. 2014). We gathered data on the number of people infected and deceased, unhealthy water bodies with malaria, the number of antimalarial dispensaries (cases recorded and/or attended to in these centers), and the provincial distribution of infected people per population size (see Table 1). One of the limitations of this historical database is that the most detailed records, which correspond to a provincial scale, only appear for the periods of 1916-1930 (deceased) and 1949 and 1954-1961 (infected). On the other hand, unhealthy bodies of water refer to floodplains that require sanitation because they are suitable for the reproduction of the vector that transmits malaria. These data come from the Directorate General of Agriculture in 1913 and 1916 and exclude those foci constituted by ricefields, hemp rafts, riverbanks, channeled streams, gutters and railroad trenches (Sousa et al. 2014).

In order to better analyse the main drivers of the eradication of autochthonous malaria in Spain during the 20th century, we studied the decrease of the disease. To this end, we first calculated the number of people deceased due to malaria with respect to the total number of annual deaths in Spain. More specifically, we calculated the quotient of the annual number of deaths by malaria (M_n) per one thousand deaths in the same year (n), including all causes of death (D_n). Equation 1 represents the quotient between these two variables:

$$I_n = M_n/1000\ D_n. \qquad \text{Equation 1}$$

Secondly, we calculated the interannual decrease of the number of deaths by autochthonous malaria with respect to the total number of deaths. More specifically, we calculated the difference in the number of deaths due to autochthonous malaria, between consecutive years, with respect to the total number of deaths, expressed in thousands, during the complete period of 1901 to 1959 (Equation 2).

$$\delta_n = (M_n - M_{n-1})/\ 1000\ M_T, \qquad \text{Equation 2}$$

where M_T is the total number of deaths due to malaria throughout the entire period analysed. The total cumulative decrease was calculated as the sum of the deviations of the reference year n with all the preceding deviations (Equation 3):

$$A_n = (\sum \delta_i) \quad \text{for } i = 1, 2, \dots n\ ;\ n \leq N, \qquad \text{Equation 3}$$

where A_n represents the cumulative increase of deaths in year *n* per every 1000 deaths for the entire period analysed. In all cases, the polynomial and/or linear regression lines related to the people who died of autochthonous malaria were calculated.

From the data of the SSIbase archive, we gathered the distribution of infected people by province capitals with respect to the total number of cases in the country (period of 1950-1959). From 1955, the information recorded in these archives was broader, including the distribution of infected people according to the size of the population centers (province capitals, centers of over 20,000 inhabitants, and centers of 20,000 inhabitants or less).

We also compared the evolution of mortality due to malaria with the main infectious diseases in Spain during the period of 1900-1959. The data were gathered from the national records of Spain stored in SSIbase by the Spanish Epidemiological Centre of the Carlos III Health Institute (Navarro 2002) between 1910 and 1945 (Table 1). This data source was also used to calculate the annual evolution of the Spanish population from 1900 to 1965. The data on the province population density and regional area occupied by greenhouse crops in 2019 were obtained from the Spanish Statistics Institute (https://www.ine.es/jaxiT3/Datos.htm?t=2852#!tabs-tabla) and the Spanish Ministry of Agriculture, Fisheries and Food (https://www.mapa.gob.es/es/estadistica/temas/estadisticas-agrarias/agricultura/esyrce/), respectively.

Trends of imported malaria during the 20th and 21st centuries

The data available in Spain on imported malaria started to be recorded in the early 1970s. However, given that some of these data are uncertain, the calculation was conducted using the cases recorded in the period of 1975-2018. These data were obtained from the Spanish epidemiological surveillance systems (SSIbase 2020), the Bulletins of the Carlos III Institute (2020), the Spanish Network of Epidemiological Surveillance (2020), and the Basic Surveillance System of the Valencian Community (2020). Herrador et al. (2019) and Sousa et al. (2020) have provided a good synthesis of these data sources, their online localization, and their limitations.

Unlike autochthonous malaria, in the case of imported malaria, there is a stable and constant record of both infected and deceased people. The number of recorded cases of people who died of imported malaria is very small and it has changed very little. For example, in 1975, there were five recorded deaths, and in 1995, there was a total of eight cases of death, for the entire country (Navarro 2002). Therefore, we calculated the interannual increase of imported malaria, during the 20th and 21st centuries, as the difference in the cases recorded every year *n* with respect to the previous year (*n-1*). Then, it was represented as the annual cumulative increase of cases of imported malaria, from the sum of the deviations of reference year *n* with all the previous deviations. Furthermore, we calculated the linear and polynomial regression lines of imported malaria patients in Spain for the period analysed. These equations allowed the trends in the increase of cases, whenever the conditions were the same as the current conditions, to be projected up to the year 2050.

The mapping of the regional distribution of imported malaria in Spain was performed with the data available in the Bulletins of the Carlos III Institute for the period of 2010-2018. The monthly evolution of the cases of imported malaria was investigated with the data provided by the Spanish Network of Epidemiological Surveillance for the periods of 2010-2016 and 2018 (there are no available records for the year 2017).

To map the provincial distribution of autochthonous malaria and the regional distribution of imported malaria, we used Geographical Information System (GIS) data. Different studies have used GIS tools to analyse the morbidity and/or mortality of malaria at the regional, national, or global scale, as well as the main drivers of the disease (Hay et al. 2002; Omumbo et al. 2002; Sipe and Dale 2003; Guerra et al. 2006; Sousa et al. 2014, 2019, 2020; Gwitira et al. 2018; Battle et al. 2019; Weiss et al. 2019). In our case, we used these tools—from the data of the years available in SSIBase—to generate the mapping of the total number of people who died of autochthonous malaria in Spain (year 1949) and the total number of people infected with imported malaria (period of 2010-2018). In these maps, we used the cartographic choropleth display method (Schiewe 2019). They were also used to represent data on the provincial population density and the area occupied by intensive greenhouse crops in the different Spanish regions. The Electronic supplementary material (ESM) includes the names of the autonomous communities or regions (see Fig. S1) and the provinces that include these regions (see Fig. S2), with the aim of making it easier for the reader to locate them on the maps presented in this study.

Data and methodology related to the climate variables

The influence of the meteorological variables on the morbidity of malaria was analysed intra- and interannually. For the interannual analysis, we selected the Meteorological Observatory of Huelva (AEMET, Spanish Meteorological Office) as representative of one of the most endemic areas of the entire country. We used the data of the mean, minimum, and maximum monthly temperatures, which were compared with the relative monthly morbidity of autochthonous malaria (monthly proportion with respect to the total annual morbidity) for the periods of 1949 and 1954-1957. This relative rate allows the data of different years with a very different number of infected people to be compared. An equivalent analysis was conducted with the monthly data of imported malaria for the period of 2010-2018. In the case of imported malaria, we used the data from the meteorological observatory of Madrid, as the largest urban population center of the country, due to its large number of infected people and its central geographic position. These data were treated in the same way as the monthly data of autochthonous malaria, with the aim of comparing the intraannual evolution of both types of malaria with respect to the mean monthly temperatures.

For the interannual analysis, we studied the correlation between the main meteorological variables (spring precipitation, summer precipitation, mean monthly precipitation of spring, and mean summer temperature) and the number of infected people attended to or recorded in the antimalarial dispensaries for the periods of 1931-1932 and 1936-1949 in the regions that were most affected by autochthonous malaria (Extremadura, Western Andalusia, and Murcia). Given that the meteorological series present several gaps in this period, we used the data obtained from the Global Climate Monitor (hereinafter, GCM). This database provides a world historic series of monthly precipitation and temperature from January 1901 to December 2016 (https://www.globalclimatemonitor.org/). Moreover, GCM allows data in cells of 0.5º x 0.5º latitude-longitude to be downloaded (Camarillo-Naranjo et al. 2019), which generates a spatial resolution that enables the detection of regional climate differences. GCM was also used to climatically classify the years with available data on the number of infected people recorded in the antimalarial dispensaries (1931-1949), using 1901-1950 as the reference period. For each of the three regions with a greater number of infected people, based on the distribution of quintiles, the years were climatically classified as very dry, dry, normal, wet, and very wet years (annual precipitation) and as very cold, cold, normal, warm, and very warm years (mean annual temperature).

Results and discussion

Drivers of autochthonous malaria during the 20th century

We represented the proportion of the total number of deaths due to autochthonous malaria, in parts per thousand, along with the evolution of the Spanish population (Fig.1).

Fig. 1 around here

From the early 20th century, there was a sharp decrease in the number of deaths due to malaria, which progressively became less pronounced with the creation of the Central Anti-Malaria Commission in 1924, until the definitive eradication of autochthonous malaria in Spain. The last death by malaria was recorded in 1959 and the last cases of infection were recorded in 1961 (Díaz et al. 2005). Throughout this period, malaria has presented episodes of epidemic peaks, with two major peaks in 1917-1922 and 1940-1944 (Fig. 1). The first epidemic peak reached its zenith in 1918 (2347 deaths) and recovered to the levels recorded before 1914 (1609 deaths) in 1922 (1518 deaths). This epidemic episode presents a relative decrease in 1918-1919, due to the increase in total mortality caused by the wrongly-called "Spanish Influenza" pandemic (Chowell et al. 2014). In 1918, the total number of deaths caused by this virus was estimated to be at least 147,114 people (Trilla et al. 2008), although other authors increase it to 230,036 deaths and highlight the coincidence of the mortality peaks of the 1918 influenza pandemic with an outbreak of malaria (Sousa et al. 2020).

There was a second peak between 1940 and 1944 after the end of the Spanish Civil War (1936-1939), which preceded the Second World War (1939-1945); during this period, the maximum number of deaths due to malaria was reached in 1942 (1781 deaths). The main drivers of this outbreak are linked to population displacements, hunger, the scarcity of antimalarial drugs, and the proliferation of anopheles due to the abandonment of antimalarial campaigns (Rico-Avelló 1950; Rodríguez-Ocaña et al. 2003; Barona and Perdiguero-Gil 2008; Sousa et al. 2014). More recent studies have analysed, separately, the spatial evolution of this epidemic peak in the different Spanish regions, concluding that the movements of both citizens and troops after the war conflict, along with the overcrowding and/or detention of population sectors in forced labor camps, contributed to intensifying this outbreak (Sousa et al. 2020). From 1947, Spain recovered to the values of 1935 (before the war conflict).

To better understand which factors act as drivers of malaria, we compared how the main infectious diseases evolved in Spain from 1910 to 1945. Regarding the epidemic peak of 1917-1922, in addition to the already mentioned partial coincidence with the 1918-1919 influenza pandemic, there were outbreaks of meningitis and tuberculosis. During the epidemic peak of 1940-1944, there were also outbreaks of syphilis and typhus. On the other hand, no statistically significant correlation was found for the period of 1910-1945 between malaria and the rest of the mentioned infectious diseases. However, after removing the two epidemic peaks of malaria from the temporal analysis, a high correlation was obtained ($R^2 = 0.81$) between malaria and typhus, as well as between malaria and syphilis ($R^2 = 0.82$) from 1920 to 1937. This suggests that there are common hygienic-sanitary and socio-economic drivers between these three infectious diseases. In this sense, it is widely known that typhus and syphilis epidemics are historically related to war conflicts and overcrowding associated with the latter (Goldmeier and Guallar 2003; Raoult et al. 2004; Tampa et al. 2014).

To better understand the inflection points of these epidemic episodes, we calculated the decrease rate of autochthonous malaria. We represented the interannual decrease of the number of deaths due to malaria (Fig. 2a) and its cumulative decrease (Fig. 2b). This decrease rate was calculated as the difference of deaths, between consecutive years, with respect to the total mortality —expressed in thousands— for the complete period of 1901 to 1959. The sections above the polynomial function indicate periods in which the mortality due to malaria began to decrease. On the other hand, the sections below the polynomial function (negative values in Fig. 2a) indicate periods in which the situation did not improve or even worsened. In this latter case, the annual decrease rate of deaths by malaria is close to zero or even negative; that is, the number of deaths increases with respect to the previous year.

Fig. 2 around here

This analysis allows the effect of the Antimalarial Commission during the period of 1924-1936 (Fig. 2a), when the lowest mortality was achieved (only 170 deaths in 1936), to be clearly appreciated. However, with the beginning of the Spanish Civil War in July 1936, the number of deaths began to rise again, increasing more rapidly during the period of 1940-1944 once the war was over. The annual decrease rate of deaths due to malaria became negative again between 1940 and 1942 (Fig. 2a); then, in 1943, it turned positive again, due to the beginning of an improvement process associated with the development and expansion of the antimalarial dispensaries (Rico-Avelló 1950; Rodríguez-Ocaña et al. 2003; Sousa et al. 2020), whose number increased from 187 in 1942 to 322 in 1946. In fact, the analysis of the relationship between the number of dispensaries and the number of malaria patients treated, only during the period of 1936-1943, displays a very high correlation (R^2 = 0.96). This clearly links the decrease of the disease to the improvement of the hygienic-sanitary conditions, without excluding an improvement of the general socio-economic conditions in the entire country.

Up to this point, the results show that, from 1940, the general deterioration of the hygienic-sanitary conditions associated with the war conflict interrupted the malaria eradication process in Spain, which was already initiated in the early 20th century. Therefore, it is worth exploring how these extraordinary conditions contributed to delaying the eradication of the disease. To solve this question, we represented the decrease rate in its cumulative form (Fig. 2b). The fit of the polynomial function (continuous line) is R^2 = 0.85; however, if we remove the values of the epidemic peak of 1940-1944, the fit of the function improves to R^2 = 0.93 (Fig. 2b). With the same data, by removing the period of 1940-1944, the eradication of autochthonous malaria in Spain could have been advanced up to the year 1951 (provided that Spain had continued the national malaria eradication programs that were being carried out before 1936). Therefore, regardless of other contemporary historical factors, the war conflict may have posed an estimated delay of 8-12 years in the eradication of autochthonous malaria in Spain with respect to other European countries, such as Austria and Finland (year 1947) or Germany and France (year 1950) (Petersen et al. 2013). Since, after the end of the Spanish Civil War conflict (1936-1939), the antimalarial fight slowed down as a consequence of the socio-economic situation, the deterioration of the national hygienic-sanitary system and the international isolation of Spain (Rico-Avelló 1950; Rodríguez-Ocaña et al. 2003). Therefore, it seems reasonable to think that this could be the main barrier to its eradication in other countries of Africa, Asia, and America, where malaria is still endemic and there are ongoing war conflicts.

Drivers of imported malaria during the 20th and 21st centuries

The data gathered in the first Spanish report on the epidemiological surveillance of transmittable diseases in 2016 highlight that 95% of the imported cases came from Africa, especially from Equatorial Guinea, Mali, Nigeria, and Senegal, among other countries (Spanish Network of Epidemiological Surveillance 2020). The most frequent profile of an infected person was that of a male (68%) within the age range of 25-54 years. The causes of travelling to the endemic regions would be linked to visits to relatives and friends, and, to a much lower extent, to migration, tourism, and business trips. These results are in agreement with studies conducted in the scope of the Community of Madrid (Rey et al. 2010).

The interannual evolution of imported malaria in Spain from the late 20th century to the 21st century shows a clear upward trend (Fig. 3). The linear fit represents a significant ascending line R^2 = 0.86 that improves when fitted to the second-degree polynomial line, which explains approximately 90% of the variance (R^2 = 0.89).

Fig. 3 around here

By extrapolating the second-order linear and polynomial functions, the interval of the cumulative total number of people infected with malaria for the year 2050 was 1100-1800 people, which is approximately double the number of cases recorded in 2018. Obviously, these are not predictive values, but only an estimation considering that the future trends were similar to the current trends.

Moreover, the impact of the pandemic caused by SARS-CoV-2 in 2020 has restricted the population movements in most of the world, so the arrival of people infected with malaria from endemic countries could decrease from 2020. This circumstance could influence the number of recorded cases of people infected with imported malaria in the same way as the 1918 influenza pandemic coincided with a peak of endemic malaria in Spain, as was mentioned in previous sections. It is difficult to analyse the causes of this phenomenon, although it is worth proposing that it could have been influenced by the deterioration of the socio-economic conditions and the saturation of the healthcare systems in early-20th century Spain. Therefore, it is also relevant to analyse—in the future—whether the COVID-19 pandemic resulted in an increase in the number of cases of autochthonous malaria in countries where it is still an endemic disease. This information could help to develop policies for the planning and prevention of infectious epidemics and pandemics, since it would allow better understandings of how the impacts of large-scale epidemic processes on national healthcare systems can affect the morbidity of other infectious diseases.

The influence of rurality and urbanization on the spatial distribution of malaria

In 1949, the distribution of the disease had a clearly rural component (Fig. 4a), since over 94% of the cases were concentrated in municipalities of 20,000 inhabitants or less (Fig. 4b).

Fig. 4 around here

The first centralized data of the provincial distribution of people infected with autochthonous malaria in Spain are from 1949. In that year, the distribution of the disease was concentrated in the westernmost provinces of Andalusia (Huelva, Seville and Cádiz, with 19,018 cases), Extremadura (5322 cases), Castilla-La Mancha (3818 cases), and Murcia (1630 cases) (Fig. 4a). The provinces of the regions of Andalusia, Extremadura, and Murcia alone represented 76.6% of all recorded cases of autochthonous malaria in that year. This coincides with the main endemic factors of endemic foci of malaria in Spain associated with other unhealthy water bodies (Western Andalusia and Ciudad Real); bad socio-economic conditions (Extremadura) (Sousa et al. 2009, 2019); and the presence of a very anthropophilic vector in Murcia (*Anopeheles labranchiae*), along with *Anopheles atroparvus*, as in the rest of the country. Unlike *Anopheles atroparvus*, which is still present, *Anopheles labranchiae* disappeared in 1973, although in 1946, it was still abundant, associated with the rice fields of Alicante and Murcia (Blázquez and Zulueta 1980; Eritja et al. 2000; Ramsadale and Snow 2000; Bueno-Marí et al. 2012). Therefore, the presence of vectors associated with unhealthy water bodies and the socio-economic conditions have been the main drivers of the main endemic foci of autochthonous malaria in Spain.

During the period of 1955-1959, 94.4% (Fig. 4b) of the recorded cases were from population centers of 20,000 inhabitants or less, and only 4% were from population centers of over 20,000 inhabitants (excluding the capitals of each province). As was previously mentioned, in 1900, 60% of the Spanish population worked in agriculture and only 13% lived in population centers of over 50,000 inhabitants (Navarro 2002). In this sense, although malaria has traditionally been a rural disease, these links are indirect and can be improved by increasing the public investment in health (Noble and Austin 2016). Recent studies in endemic areas of Brazil also show the importance of the urbanization/rurality gradient for explaining the distribution of the disease (Lana et al. 2017).

On the other hand, imported malaria in Spain in the 21st century seems to be associated with those regions with a greater population concentration (e.g., the Community of Madrid, Catalonia, and the Valencian Community; Fig. 5a), although this also appears to be influenced by the proximity to large areas associated with intensive greenhouse agriculture (Fig. 5b).

Fig. 5 around here

The cases of imported malaria were concentrated around the main cities and conurbations of Spain. During the period of 2010-2018, most of the cases were concentrated in the regions of Madrid and Catalonia (42% of all the cases in Spain). This trend remained constant during the second decade of the 21th century in all regions. In 2018, Catalonia and Madrid alone comprised 31.6% (270 cases) and 19.9% (170 cases) of the reported cases, respectively, followed by Andalusia (10.4%, 89 cases) and the Valencian Community (8.7%, 74 cases).

Comparing the distribution of the recorded cases of imported malaria at the regional scale (Fig. 5a) with the provincial population density (Fig. 5b), there is a clear parallelism associated with the most densely populated cities and their conurbations, such as Madrid, Barcelona, Valencia, Seville, Zaragoza, Málaga, Murcia, etc. It is also important to note that these urban nuclei coincide with nodes of communication and the exchange of international travelers (airports, etc.). In some cases, the relationship with the population density is not so obvious. This is why we added the available regional data of intensive greenhouse crops (Fig. 5b), which are mainly concentrated in some areas of Andalusia, Murcia, the Valencian Community, Catalonia, and Aragon, where the presence of seasonal workers, many of whom come from malaria-endemic countries, could help to explain the concentration of cases in these regions. Future studies, using more disaggregated data of infected people and crops at the provincial or even local scale, could help to better understand the true weight of these agricultural campaigns and whether they have a significant influence on the seasonal peaks of imported malaria.

To further delve into the drivers that intervene in this disease, we analysed the role of climatic variables from two different perspectives: the variation of the disease at intraannual and interannual scales.

Climatic factors related to malaria at the intraannual scale

To establish measures for the prevention and follow-up of infectious diseases with a seasonal component, such as malaria, it is very useful to know the seasonal variation of the number of infected people and its fluctuations between consecutive years. This information can help to improve the planning and management of the available sanitary resources and establish surveillance programmes that fit better to the seasonal periods with a greater number of cases. The evolution of the monthly relative morbidity presents very pronounced seasonal peaks in the case of both autochthonous (Fig. 6a) and imported malaria (6b).

Fig. 6 around here

The seasonal distribution, in the case of autochthonous malaria, shows a centered unimodal bell during the summer period (beginning of July), with the tails of the distribution occurring toward the end of spring and beginning of autumn (Fig. 6a). Imported malaria also presents a unimodal bell-shaped intraannual distribution, with a maximum value at the beginning of autumn (Fig. 6b), although this distribution is less symmetrical than that of autochthonous malaria. This indicates an average delay of two months with respect to the distribution of autochthonous malaria in Spain. This gap suggests that the thermal meteorological variables may play a role as drivers, at least in a coadjuvant manner, only in the case of autochthonous malaria. To corroborate this, we analysed the relationship between the mean monthly temperatures of these periods and the monthly relative morbidity rate of autochthonous malaria (Fig. 7a) and imported malaria (Fig. 7b).

Fig. 7 around here

There is a clear seasonality in the spread of autochthonous malaria during the summer months (R^2 = 0.88) (Fig. 7a). When we associated the number of infected people with the maximum and minimum temperature for the same period, strong correlations were obtained (R^2 = 0.84 and R^2 = 0.88, respectively). However, a different result was obtained in the case of imported malaria (Fig. 7b), since the correlation (R^2 = 0.33) was much weaker for a similar sample size. This is due to the displacement in the maximum peak of infected people from summer to autumn (Fig. 6b). Since this gap is not directly related to the temperature, this suggests that other factors that are not directly linked to climatology could be involved, including the date of displacement of the infected people from the endemic countries to Spain in the post-vacation period (after the summer in the Mediterranean region). Although, in the countries of origin, the peak of the disease occurs during the warmer months, the displacements due to migration or tourism can take place more frequently during the summer or even later, so the symptoms could be detected, to a greater extent, at the beginning of autumn.

On the other hand, the correlation obtained in the case of autochthonous malaria (Figure 7a) is related to the temperature required for the development of both the vector and the parasite that causes the infection. This aspect is relevant for the transmission of malaria, since the average environmental temperature of 24 hours determines whether the extrinsic life cycle of the parasite can take place in the anophelines (Petersen et al. 2013). The optimal temperature range for the development of the parasite *Plasmodium vivax* inside the mosquito is 16-33 ºC (Piperaki and Daikos 2016). Above a sustained temperature of 38 ºC, there is no transmission of the parasite (Díaz et al. 2005). This explains why the greatest mean annual morbidity rates occur in the months that are more favorable to the completion of the corresponding biological cycles (Fig. 6a) and with an optimal mean monthly temperature of 20-30 ºC (Fig. 7). The coefficient of determination indicates that, in the annual cycle, almost 90% of the variability of the morbidity of autochthonous malaria is explained by temperature. This covariation does not necessarily imply causality, although it does indicate that the thermal conditions establish some limits to the optimal development of both the vector and the protozoon that transmits this disease. Therefore, in this case, temperature could act as a rather limiting factor or a factor that, under conditions of spread or epidemic due to other drivers, increases the rate of infected people during epidemic outbreaks.

Climatic factors related to malaria at the interannual scale

If the climatic conditions act as a limiting factor or coadjuvate in the expansion of the epidemic outbreaks of autochthonous malaria, this must be shown by the historical records of morbidity. Although there are national records of deaths from 1900 and infected people from 1943, these data cannot be spatially assigned, since they refer to the whole of the country. This is a fundamental problem that must be overcome in order to analyse the role of the meteorological variables, since Spain is a country characterized by strong variations in temperature and precipitation due to its latitude, longitude, and orography.

One alternative is provided by a recent study that shows the possibility of using antimalarial dispensaries to geolocalize the foci of malaria (Sousa et al. 2020). During the period of 1943-1959, from which there are data on both the total number of infected people and the total number of deaths in the whole country, the coefficient between these two variables is very high (R^2 = 0.95). The Case Fatality Rate (CFR) for the period of 1943-1954 was 0.34%. Therefore, both variables can be used as a reference for the spread of malaria. According to Navarro (2002), there are only national records on the number of infected people from 1943, although—separately— we have found records on the number of infected people in the antimalarial dispensaries distributed all over the country for the periods of 1931-1932, 1936-1949, and 1953-1961.

By comparing the data of infected people in the entire country with those recorded in the antimalarial dispensaries for the period with available records (1943-1949 and 1953-1961), a very good fit was obtained (R^2 = 0.998). Both information sources measured the same parameters with small discrepancies, likely due to administrative causes or the management of data in the. Since these two variables are closely related, it is possible to use the data of infected people from the antimalarial dispensaries as a tool for studying how the thermal variables affected the evolution of the disease during the period of 1931-1949. The regions that were most affected by autochthonous malaria in Spain were Extremadura, Western Andalusia, and Murcia (see ESM Table S1). During the period of 1931-1949, a mean annual total of 130,752 people infected with malaria were treated in Spain, of whom 90,950 came from the three mentioned regions. In fact, these three regions concentrated 56.5-93.6% of the cases from 1931 to 1949.

As was previously described, the intraannual seasonality of the number of infected people appears to be mainly associated with summer (Fig. 6a). Therefore, we selected the precipitation and temperature of summer and spring (Table 2) to analyse its relationship with the number of infected people of each of these historically endemic regions.

Table 2 around here

In general, the sample size does not allow reliable conclusions to be drawn; in any case, the behavior is not homogeneous in the three regions (see Table ~~3~~2). Some of these differences are due to the fact that these regions are climatically different. Generally, the behavior of the Atlantic areas (Western Andalusia) is very different from that of the Mediterranean areas (Murcia). In turn, the effect of continentality (in the case of Extremadura), along with the topography, explains these differences. Nevertheless, the effect of the climatic factors did not seem to affect the morbidity of autochthonous malaria in Spain. In the specific case of Murcia, the Pearson's correlation coefficient for spring precipitation (-0.537) is associated with the fact that the period of 1946-1949, when the eradication of the disease began, coincides with very wet years in this region (1946-1949).

Therefore, the results show that there is no clear correlation between the number of infected people in the main endemic regions of Spain and the climatic variables analysed (Table 2). However, the climatic conditions may intervene as coadjuvants of other drivers of the disease. To analyse this aspect, we compared the quintiles of temperature and precipitation (see ESM Table S2) with the number of infected people during the period of 1931-1949 in Western Andalusia, Extremadura and Murcia.

When jointly analyzing the results of tables S1 and S2 of the ESM it is shown that, globally, the epidemic periods occurred when there were favorable climatic conditions for the development and transmission of autochthonous malaria. However, when the hygienic-sanitary conditions began to improve, the climatic conditions did not seem to be a relevant barrier to the eradication of the disease. In Western Andalusia, the years of the maximum increase in the number of infected people (1940-1943, see ESM Table S1) coincide with warm and very warm years and include several very wet years (1941-1942; see ESM Table S2). The most interesting aspect is that, during the period of 1936-1943, the number of infected people increased progressively, which coincides with the fact that all the years of this period were warm or very warm (in fact, the annual mean temperature and the number of infected people obtained $R^2 = 0.43$). From the year 1944, the number of infected people decreased in Western Andalusia due to the improvement of the economic and sanitary conditions after the Spanish post-war, despite the fact that the climate was still warm or very warm, although slightly drier.

In the region of Extremadura, the years of the maximum increase in the number of infected people (1940-1943; see ESM Table S1) were mostly warm or very warm and, in general, rather wet (see ESM Table S2). From the year 1944, the number of infected people decreased rapidly, due to the improvement of the hygienic-sanitary conditions, despite corresponding to warm or very warm years. In the region of Murcia, the years of the maximum increase in the number of infected people were 1943-1944 (see ESM Table S1). The year 1943 was warm and wet, but 1944 was cold and dry (see ESM Table S2). From the year 1944, and especially 1945, the number of infected people decreased substantially, due to the fight against malaria, although there is no clear pattern associated with temperature, since the climatic conditions were still favorable for the development of the disease.

Conclusions

During the 20th century, the main drivers that regulated the morbidity and mortality of autochthonous malaria in Spain were the socio-economic and hygienic-sanitary conditions. However, the endemic foci were strongly associated with the presence of vast areas occupied by unhealthy water bodies (Western Andalusia, Southern Spain, and Ciudad Real), the existence of malaria-transmitting vectors (especially *Anopheles labranchiae* in the case of Murcia and Alicante), and worse socio-economic conditions (Northern Extremadura). The epidemic outbreak of 1917-1922 was more intense by overcrowding of the Spanish healthcare system, as a consequence of the pandemic flu. Instead, the epidemic outbreak of 1940-1944 was generated by the consequences of the war conflict (movement of troops, deterioration of the sanitary conditions, abandonment of the fight against malaria, the hunger and scarcity of drugs associated with the international isolation, and the overcrowding of war prisoners and troops).

However the drivers of imported malaria during the 20th century and, especially during the 21st century, seem to be linked to the higher international mobility of the population, especially associated with family visits to endemic countries of Africa (Rey et al. 2010), with some of them having strong relations to colonial and/or cultural origins, such as Equatorial Guinea. In the case of imported malaria, the key factor is being close to large cities and suburbs, which, in addition, include the main international communication nodes. For this reason, malaria has evolved from a rural disease during the first half of the 20th century (autochthonous malaria) to an urban area related disease during the 21st century (imported malaria). It will not be possible to limit the progressive increase of imported malaria, in Spain and other Mediterranean countries, as long as it is not possible to eradicate autochthonous malaria in the rest of the world.

The climatic factors did not play a relevant role as drivers of autochthonous malaria in Spain during the 20th and 21st centuries (at least directly, as is shown by the poor correlation with the thermal variables in the 21st century). However, they have conditioned the disease seasonality. Furthermore during the epidemic outbreak of 1940-1944, the climatic conditions were optimal for the spread of this outbreak. In this sense, during periods of the 20th century, the thermal conditions created favorable periods for the spread of autochthonous malaria, thus coadjuvating the spread of the disease. In this sense, the results of this study show that the epidemic outbreaks of malaria can be influenced by the local climate. Nevertheless, it is much more complex to establish how they will be affected by climate change in the long term (Patz et al. 2002), since their effects are not always linear and coexist with other non-climatic drivers, which can be more relevant in transmission of the disease.

Determining the historical drivers of malaria can help to better understand the risk of the disease and establish future prevention measures. To this end, it would be very interesting to conduct comparative analyses of the seasonality of the disease in countries of the whole Mediterranean region. Although the situation in Europe with respect to the eradication of malaria is very good, the deterioration of healthcare services due to a catastrophe or wars can favor the relapse of malaria (Bruce-Chwatt and De Zulueta 1980; WHO 2006). In the late 20th century, the local transmission of malaria had reestablished in the Caucasus, the republics of Central Asia and, to a lesser extent, the Russian Federation, after the war in Afghanistan and the dissolution of the Soviet Union. In Turkey, a sharp increase in the number of cases of malaria in the 1990s was associated with a large migratory movement of refugees from Iraq during the First Gulf War (WHO 2016; Berglar and Vembar 2019).

Changes in the economic conditions and budget cuts in the national healthcare systems of European countries, associated with the economic crisis of 2008, can also contribute to the relapse of already eradicated infectious diseases such as malaria (Andriopoulos et al. 2013; Danis et al 2013; Karanikolos et al. 2013; Smith et al. 2014). In fact, one of the lessons from the past is the increase of endemic malaria in Spain during the pandemic flu of 1918. Future studies will have to determine whether the overcrowding of healthcare systems due to the COVID-19 pandemic is a key factor for the prevalence of malaria in countries where it is still endemic. Some aspects that may have a negative influence on this are (1) the fact that both infections share several easily recognizable symptoms (Chanda-Kapata et al. 2020), which may lead to undervaluing the presence of some of these infections (or even co-infections; Ray et al. 2020); (2) the abandonment of antimalarial treatment and follow-ups; and (3) limitations in the supplies of antimalarial drugs (Di Gennaro et al. 2020; Nghochuzie et al. 2020).

Acknowledgements

We want to thank the comments and suggestions of reviewers that have helped us to improve the MS.

Conflicts of Interest

The authors declare no conflict of interest.

References

Andriopoulos P, Economopoulou A, Spanakos G, Assimakopoulos G (2013) A local outbreak of autochthonous *Plasmodium vivax* malaria in Laconia, Greece-a re-emerging infection in the southern borders of Europe? Int J Infect Dis 17: e125-e128. https://doi.org/10.1016/j.ijid.2012.09.009

Barona JL, Perdiguero-Gil E (2008) Health and the war. Changing schemes and health conditions during the Spanish civil war. Dynamis 28:103–126. https://doi.org/10.4321/s0211-95362008000100005

Basic Surveillance System of the Valencian Community. Available online: http://www.sp.san.gva.es/DgspPortal/docs/epidemiologia/casos_tasas_anuales.htm (accessed on 7 April 2020).

Battle KE, Lucas TCD, Nguyen M, et al (2019) Mapping the global endemicity and clinical burden of *Plasmodium vivax*, 2000–17: a spatial and temporal modelling study. Lancet 394:332–343. https://doi.org/10.1016/S0140-6736(19)31096-7

Berglar AV, Vembar SS (2019) Past, present and future of malaria prevalence and eradication in the light of climate change. In: Encyclopedia of Environmental Health. Elsevier, pp 49–67

Blazquez J, De Zulueta J (1980) The disappearance of *Anopheles labranchiae* from Spain. Parassitologia 22:161–3

Bruce-Chwatt LJ, Zulueta J (1980) The rise and fall of malaria in Europe : a historico-epidemiological study, Published. Oxford University Press, Walton Street, Oxford OX2 6DP

Bueno-Marí R, Bernués-Bañeres A, Jiménez-Peydró R (2012) Updated checklist and distribution maps of mosquitoes (Diptera: Culicidae) of Spain. Eur Mosq Bull 30:91–126. https://www.researchgate.net/profile/Ruben_Bueno_Mari/publication/287181603_Updated_checklist_and_distribution_maps_of_mosquitoes_Diptera_Culicidae_of_Spain/links/56779b8508ae502c99d3e3a8/Updated-checklist-and-distribution-maps-of-mosquitoes-Diptera-Culicidae-of-Spain.pdf

Bulletins of the Carlos III Institute (2020) Available online: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Boletines/Paginas/BoletinSemanalEnRed.aspx (accessed on 7 April 2020).

Camarillo-Naranjo JM, Álvarez-Francoso JI, Limones-Rodríguez N, et al (2019) The global climate monitor system: from climate data-handling to knowledge dissemination. Int J Digit Earth 12:394–414. https://doi.org/10.1080/17538947.2018.1429502

Chanda-Kapata P, Kapata N, Zumla A (2020) COVID-19 and malaria: A symptom screening challenge for malaria endemic countries. Int. J. Infect. Dis. 94:151–153.

https://doi.org/10.1016/j.ijid.2020.04.007

Chowell G, Erkoreka A, Viboud C, Echeverri-Dávila B (2014) Spatial-temporal excess mortality patterns of the 1918-1919 influenza pandemic in Spain. BMC Infect Dis 14:371. https://doi.org/10.1186/1471-2334-14-371

Danis K, Lenglet A, Tseroni M, et al (2013) Malaria in Greece: Historical and current reflections on a re-emerging vector borne disease. Travel Med. Infect. Dis. 11:8–14. https://doi.org/10.1016/j.tmaid.2013.01.001

Di Gennaro F, Marotta C, Locantore P, et al (2020) Malaria and COVID-19: Common and Different Findings. Trop Med Infect Dis 5:141. https://doi.org/10.3390/tropicalmed5030141

Díaz J, Ballester F, López-Vélez R (2005) Impacts on human health. In: Moreno Rodríguez JM (ed) A preliminary general assessment of the impacts in Spain due to the effects of climate change. Ministerio de Medio Ambiente, Madrid, pp 699–741

Eritja R, Aranda C, Padrós J, et al (2000) An annotated checklist and bibliography of the mosquitoes of Spain (Diptera: Culicidae). Eur Mosq Bull 8:10–18. https://www.cabdirect.org/cabdirect/abstract/20003035086

Fernández Astasio B (2003) La erradicación del paludismo en España : aspectos biológicos de la lucha antipalúdica. Universidad Complutense de Madrid, Servicio de Publicaciones

Goldmeier D, Guallar C (2003) Syphilis: An update. Clin. Med. (Northfield. Il). 3:209–211. https://doi.org/10.7861/clinmedicine.3-3-209

Guerra CA, Snow RW, Hay SI (2006) Mapping the global extent of malaria in 2005. Trends Parasitol 22:353–358. https://doi.org/10.1016/j.pt.2006.06.006

Gwitira I, Murwira A, Masocha M, et al (2019) GIS-based stratification of malaria risk zones for Zimbabwe. Geocarto Int 34:1163–1176. https://doi.org/10.1080/10106049.2018.1478889

Hay SI, Cox J, Rogers DJ, et al (2002) Regional warming and malaria resurgence: Commentary. Nature 420:628. https://doi.org/10.1038/420628a

Herrador Z, Fernández-Martínez B, Quesada-Cubo V, et al (2019) Imported cases of malaria in Spain: Observational study using nationally reported statistics and surveillance data, 2002-2015. Malar. J. 18:230. https://doi.org/10.1186/s12936-019-2863-2

Hertig E (2019) Distribution of *Anopheles* vectors and potential malaria transmission stability in Europe and the Mediterranean area under future climate change. Parasites and Vectors 12:18.

https://doi.org/10.1186/s13071-018-3278-6

Iriso A, Bueno-Marí R, De las Heras E, et al (2017) Cambio climático en España y su influencia en las enfermedades de transmisión vectorial. Rev Salud Ambient 17:70–86. https://zaguan.unizar.es/record/70016/files/texto_completo.pdf

Karanikolos M, Mladovsky P, Cylus J, et al (2013) Financial crisis, austerity, and health in Europe. Lancet 381:1323–1331. https://doi.org/10.1016/S0140-6736(13)60102-6

Lana RM, Riback TIS, Lima TFM, et al (2017) Socioeconomic and demographic characterization of an endemic malaria region in Brazil by multiple correspondence analysis. Malar J 16:397. https://doi.org/10.1186/s12936-017-2045-z

López-Vélez R, Molina R (2005) Cambio climático en España y riesgo de enfermedades infecciosas y parasitarias transmitidas por artrópodos y roedores. Rev. Esp. Salud Publica 79:177–190

Navarro M, Navaza B, Guionnet A, López-Vélez R (2012) Chagas disease in Spain: need for further public health measures. PLoS Negl Trop Dis 6:e1962. https://doi.org/10.1371/journal.pntd.0001962

Navarro R (2002) Análisis de la sanidad en España a los largo del siglo XX. Madrid. Instituto de Salud Carlos III (Ministerio de Sanidad)

Nghochuzie NN, Olwal CO, Udoakang AJ, et al (2020) Pausing the fight against malaria to combat the COVID-19 pandemic in Africa: is the future of malaria bleak? Front Microbiol 11:1476. https://doi.org/10.3389/fmicb.2020.01476

Noble MD, Austin KF (2016) Rural disadvantage and malaria in less-developed nations: a cross-national investigation of a neglected disease. Rural Sociol 81:99–134. https://doi.org/10.1111/ruso.12087

Omumbo JA, Hay SI, Goetz SJ, et al (2002) Updating historical maps of malaria transmission intensity in East Africa using remote sensing. Photogramm. Eng. Remote Sensing 68:161–166

Patz JA, Hulmet M, Rosenzweig C, et al (2002) Climate change: Regional warming and malaria resurgence. Nature 420:627–628. https://doi.org/10.1038/420627a

Petersen E, Severini C, Picot S (2013) *Plasmodium vivax* malaria: a re-emerging threat for temperate climate zones? Travel Med Infect Dis 11:51–59. https://doi.org/10.1016/j.tmaid.2013.01.003

Piperaki ET, Daikos GL (2016) Malaria in Europe: emerging threat or minor nuisance? Clin. Microbiol. Infect. 22:487–493. https://doi.org/10.1016/j.cmi.2016.04.023

Pletsch D (1965) Informe sobre una misión efectuada en España en septiembre-noviembre de 1963 destinada a la certificación de la erradicación del paludismo. Rev Sanid Hig Publica (Madr) 39:309–367

Ramsdale C, Snow K (2000) Distribution of the genus *Anopheles* in Europe. Eur Mosq Bull 1–26

Raoult D, Woodward T, Dumler JS (2004) The history of epidemic typhus. Infect. Dis. Clin. North Am. 18:127–140. https://doi.org/10.1016/S0891-5520(03)00093-X

Ray M, Vazifdar A, Shivaprakash S (2020) Co-infection with malaria and coronavirus disease-2019. J Glob Infect Dis 12:162. https://doi.org/10.4103/jgid.jgid_160_20

Rey S, Zuza I, Martínez-Mondéjar B, et al (2010) Imported malaria in an area in southern Madrid, 2005-2008. Malar J 9:. https://doi.org/10.1186/1475-2875-9-290

Rico-Avelló C (1950) La epidemia de paludismo de la postguerra. Rev Sanid Hig Publica (Madr) 24:701–737. https://pubmed.ncbi.nlm.nih.gov/14816802/

Rodríguez-Ocaña E, Ballester Añón R, Perdiguero Gil E, et al (2003) La accion medico-social contra el paludismo en la Espana metropolitana y colonial del siglo XX. Consejo Superior de Investigaciones Científicas, Madrid

Schiewe J (2019) Empirical studies on the visual perception of spatial patterns in choropleth maps. KN - J Cartogr Geogr Inf 69:217–228. https://doi.org/10.1007/s42489-019-00026-y https://doi.org/10.1007/s42489-019-00026-y

Sipe NG, Dale P (2003) Challenges in using geographic information systems (GIS) to understand and control malaria in Indonesia. Malar J 2:1–8. https://doi.org/10.1186/1475-2875-2-1

Smith KR, Woodward A, Campbell-Lendrum D, et al (2014) Human health: Impacts, adaptation, and co-benefits. In: Climate Change 2014 Impacts, Adaptation and Vulnerability: Part A: Global and Sectoral Aspects. Cambridge University Press, pp 709–754

Sousa A, Andrade F, Félix A, et al (2009) Historical Importance of Wetlands in Malaria Transmission in Southwest of Spain. Limnetica 28:283–300. https://idus.us.es/bitstream/handle/11441/34460/Historical%20importance.pdf?sequence=4&isAllowed=y

Sousa A, García-Barrón L, Vetter M, Morales J (2014) The historical distribution of main malaria foci in Spain as related to water bodies. Int J Environ Res Public Health 11:7896–7917. https://doi.org/10.3390/ijerph110807896

Sousa A, García-Barrón L, Aguilar-Alba M, Vetter M, Morales J (2019) The importance of wetlands and unhealthy water bodies in the distribution of malaria in Spain. In: Chaminé H, Barbieri M, Kisi O, Chen M, Merkel B (eds) Advances in Sustainable and Environmental Hydrology, Hydrogeology, Hydrochemistry and Water Resources, pp. 77-79. Springer, Cham. https://doi.org/10.1007/978-3-030-01572-5_19

Sousa A, Aguilar-Alba M, Vetter M, et al (2020) Spatiotemporal distribution of malaria in Spain in a global change context. Atmosphere 11:346. https://doi.org/10.3390/atmos11040346

Spanish Network of Epidemiological Surveillance (2020) Available online: https://publicaciones.isciii.es/unit.jsp?unitId=cne (accessed on 7 April 2020).

SSIbase (2020) Annual Reports of the Spanish Statistical Institute (SSIbase). Available online: https://www.ine.es/inebaseweb/libros.do?tntp=25687 (accessed on 7 April 2020).

Tampa M, Sarbu I, Matei C, et al (2014) Brief history of syphilis. J. Med. Life 7:4–10

Tatem AJ, Jia P, Ordanovich D, et al (2017) The geography of imported malaria to non-endemic countries: a meta-analysis of nationally reported statistics. Lancet Infect Dis 17:98–107. https://doi.org/10.1016/S1473-3099(16)30326-7

Trilla A, Trilla G, Daer C (2008) The 1918 "Spanish Flu" in Spain. Clin Infect Dis 47:668–673. https://doi.org/10.1086/590567

Weiss DJ, Lucas TCD, Nguyen M, et al (2019) Mapping the global prevalence, incidence, and mortality of *Plasmodium falciparum*, 2000–17: a spatial and temporal modelling study. Lancet 394:322–331. https://doi.org/10.1016/S0140-6736(19)31097-9

WHO (2006) From malaria control to elimination in the WHO European region 2006–2015. World Health Organization,Regional Office for Europe, Copenhagen, Denmark

WHO (2016) History of malaria elimination in the European Region. World Health Organization, Copenhagen, Denmark

WHO (2019) World malaria report 2019. World Health Organization

Zhao X, Smith DL, Tatem AJ (2016) Exploring the spatiotemporal drivers of malaria elimination in Europe. Malar J 15:122. https://doi.org/10.1186/s12936-016-1175-z

Table 1 General synthesis of the data sources used in this study. The column of the temporal period shows the years presented in the results (in some cases, the analysed data were broader, although they were not included, as they presented some methodological limitations)

Results		Source	Spatial extension	Temporal period (years)
Autochthonous malaria	Number of deaths due to malaria with respect to the total annual number of deaths	Database of the Spanish Statistics Institute	Spain	1900-1965
	Annual rate of mortality decrease and cumulative annual rate of mortality decrease	Database of the Spanish Statistics Institute	Spain	1900-1959
	Spatial distribution of the number of infected people	Database of the Spanish Statistics Institute	Spain (provincial)	1949
	Distribution of the number of infected people with respect to the size of the population	Database of the Spanish Statistics Institute	Spain	1955-1959
	Monthly distribution of the number of infected people	Database of the Spanish Statistics Institute	Spain	1949 and 1954-1956
	Relationship between the mean monthly temperature and the total number of infected people	Database of the Spanish Statistics Institute Meteorological Observatory of Huelva (AEMET)	Spain (Huelva))	1949, 1954-1957
	Number of patients attended to or registered in the antimalarial dispensaries	Database of the Spanish Statistics Institute	Spain (regional)	1931-1949
	Relationship between the number of patients attended to or registered in the antimalarial dispensaries and meteorological variables	Database of the Spanish Statistics Institute Global Climate Monitor	Spain (regional)	1931-1932 and 1936-1949
Other infectious diseases	Number of deaths due to tuberculosis, meningitis, influenza, measles, diphtheria, smallpox, scarlet fever, syphilis, and typhus	Database of the Spanish Statistics Institute Navarro (2002)	Spain	1910-1945
Imported malaria	Cumulative rate of annual increase of the number of infected people	Bulletins of the Instituto Carlos III Spanish Network of Epidemiological Surveillance Sistema Básico de Vigilancia Comunitat Valenciana (Basic Surveillance System of the Comunitat Valenciana)	Spain	1975-2018
	Spatial distribution of the number of infected people	Bulletins del Instituto Carlos III	Spain (regional)	2010-2018
	Monthly distribution of the number of infected people	Spanish Network of Epidemiological Surveillance	Spain	2010-2016 and 2018
	Relationship between the mean monthly temperature and the total number of infected people	Spanish Network of Epidemiological Surveillance Meteorological Observatory of Madrid (European Climate Assessment and Dataset (ECA&D))	Spain (Madrid)	2010-2018
Current climate trends	Analysis of quintiles of the mean annual temperature	Global Climate Monitor	Spain (regional)	1931-1949
	Analysis of quintiles of the annual precipitation	Global Climate Monitor	Spain (regional)	1931-1949

Table 2 Pearson's correlation coefficient between the number of people infected with autochthonous malaria recorded in the antimalarial dispensaries and the regional meteorological variables for the period of 1931-1949 (there are no data of infected people for the period of 1933-1935)

Region	Spring precipitation	Summer precipitation	Mean spring temperature	Mean summer temperature
Western Andalusia	0.258	0.145	0.072	0.325
Extremadura	0.0001	0.182	-0.018	0.281
Murcia	-0.537	0.346	-0.446	0.187

Legends of figures

Fig. 1 Number of deaths due to malaria in Spain with respect to the total annual mortality (x1000) and population for the period of 1900-1965 and the polynomial function that it fits to.

Fig. 2 a Annual decrease rate of deaths due to malaria in Spain (1900-1951) and its polynomial function. **b** Cumulative annual rate of deaths due to malaria in Spain (1900-1951) and its polynomial function (continuous line and light green color). The dark green dashed line represents the polynomial function after removing the epidemic peak of the Spanish post-war period

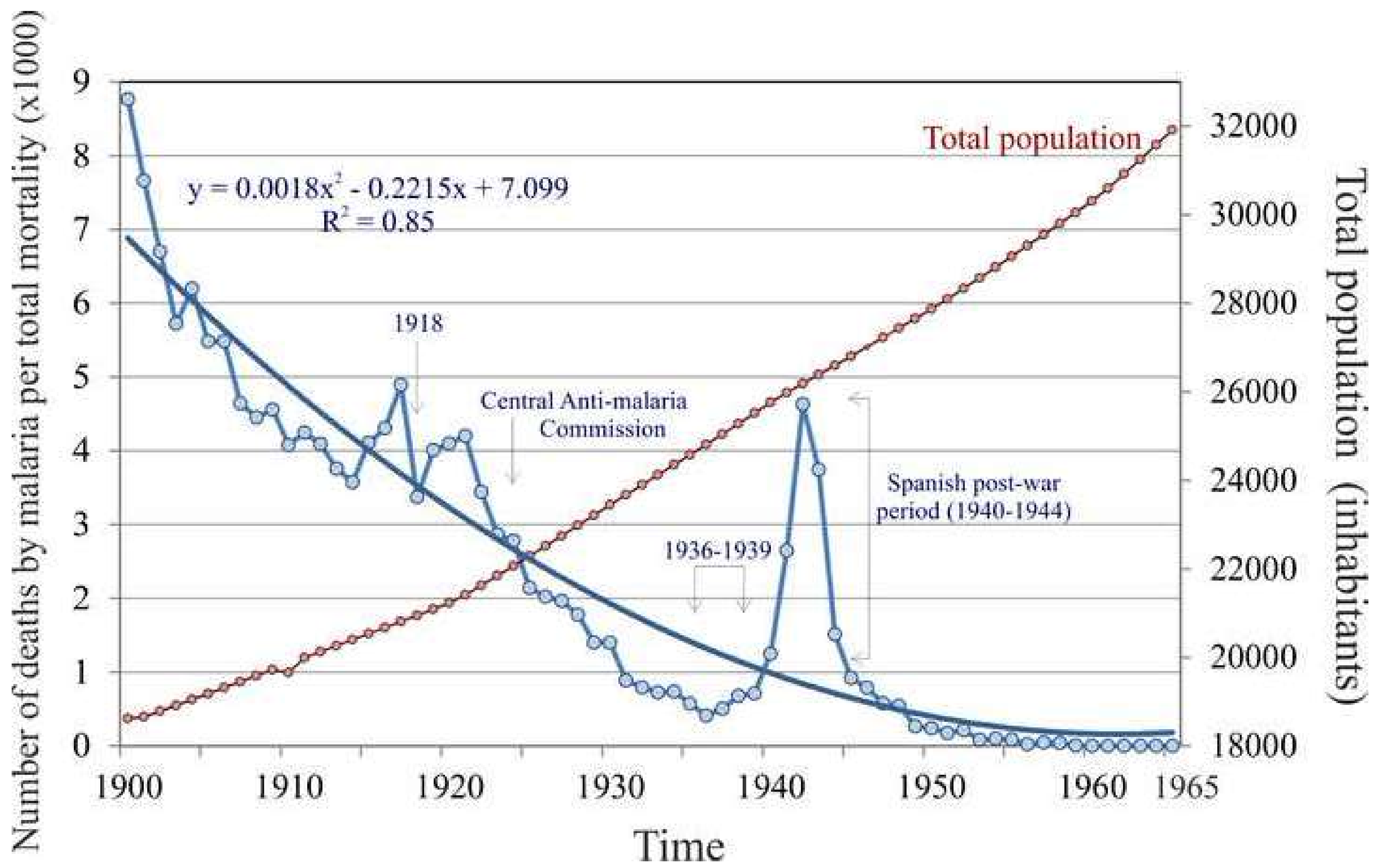
Fig. 3 Cumulative annual increase rate of people infected with imported malaria in Spain from 1975 to 2018 and its linear (green dashed line) and polynomial (blue dashed line) regression lines.

Fig. 4 a Provincial distribution of people infected with autochthonous malaria in Spain in 1949 (modified and expanded from Sousa et al. (2020). **b** Diagram of sectors showing the distribution of the number of people infected with malaria in Spain during the period of 1955-1959, according to the size of the population centers

Fig. 5 a Regional distribution of people infected with imported malaria in Spain during the period of 2010-2018. **b** Provincial distribution of the population density and areas occupied by greenhouse crops in 2019

Fig. 6 a) Seasonal distribution of autochthonous malaria in Spain during the periods of 1949 and 1954-1956. **b)** Seasonal distribution of imported malaria in Spain during the periods of 2010-2016 and 2018

Fig. 7 a Dispersion diagram of the mean monthly temperature in the observatory of Huelva (SW Spain) and the monthly relative morbidity of autochthonous malaria for the period of 1949-1957 in Spain. **b** Dispersion diagram of the mean monthly temperature in the observatory of Madrid (central Spain) and the monthly relative morbidity of imported malaria for the period of 2010-2018 in Spain



Number of deaths by malaria per total mortality (x1000)
9
8
7
6
5
4
3
2
1
0
y = 0.0018x² - 0.2215x + 7.099
R² = 0.85
1918
Central Anti-malaria
Commission
1936-1939
Spanish post-war
period (1940-1944)
Total population
32000
30000
28000
26000
24000
22000
20000
18000
Total population (inhabitants)
1900
1910
1920
1930
1940
1950
1960
1965
Time

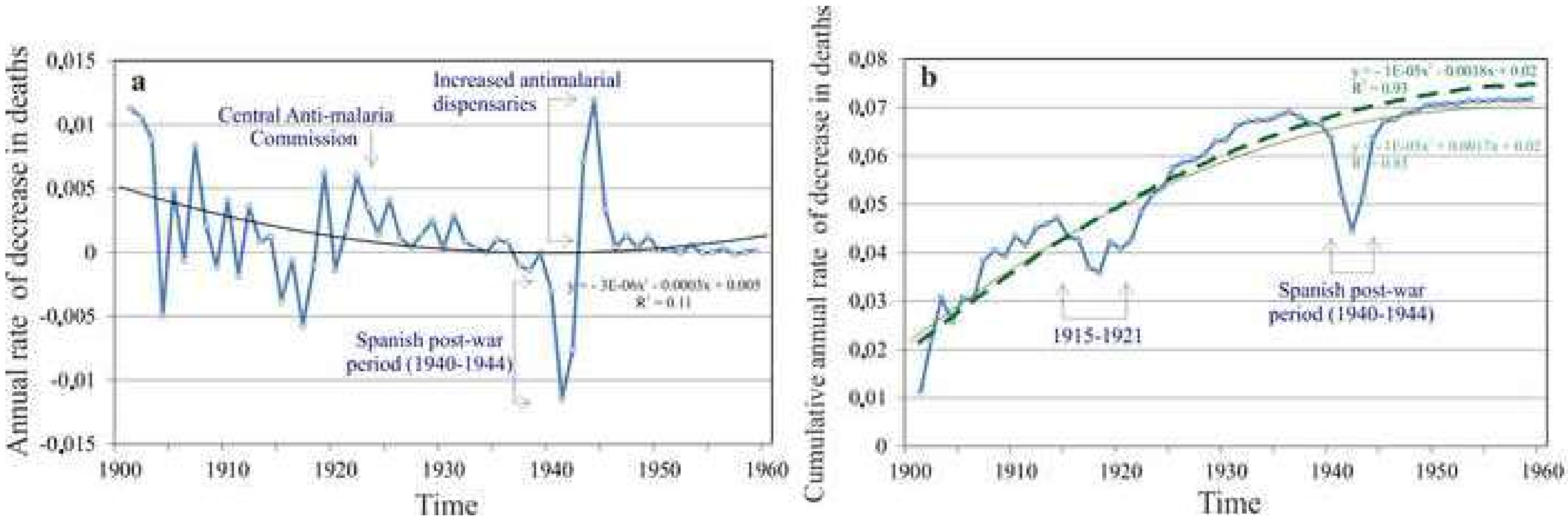

a
Annual rate of decrease in deaths
0,015
0,01
0,005
0
-0,005
-0,01
-0,015
1900
1910
1920
1930
1940
1950
1960
Time
Central Anti-malaria Commission
Increased antimalarial dispensaries
Spanish post-war period (1940-1944)
b
Cumulative annual rate of decrease in deaths
0,08
0,07
0,06
0,05
0,04
0,03
0,02
0,01
0
1915-1921
Spanish post-war period (1940-1944)

Figure 3 colour

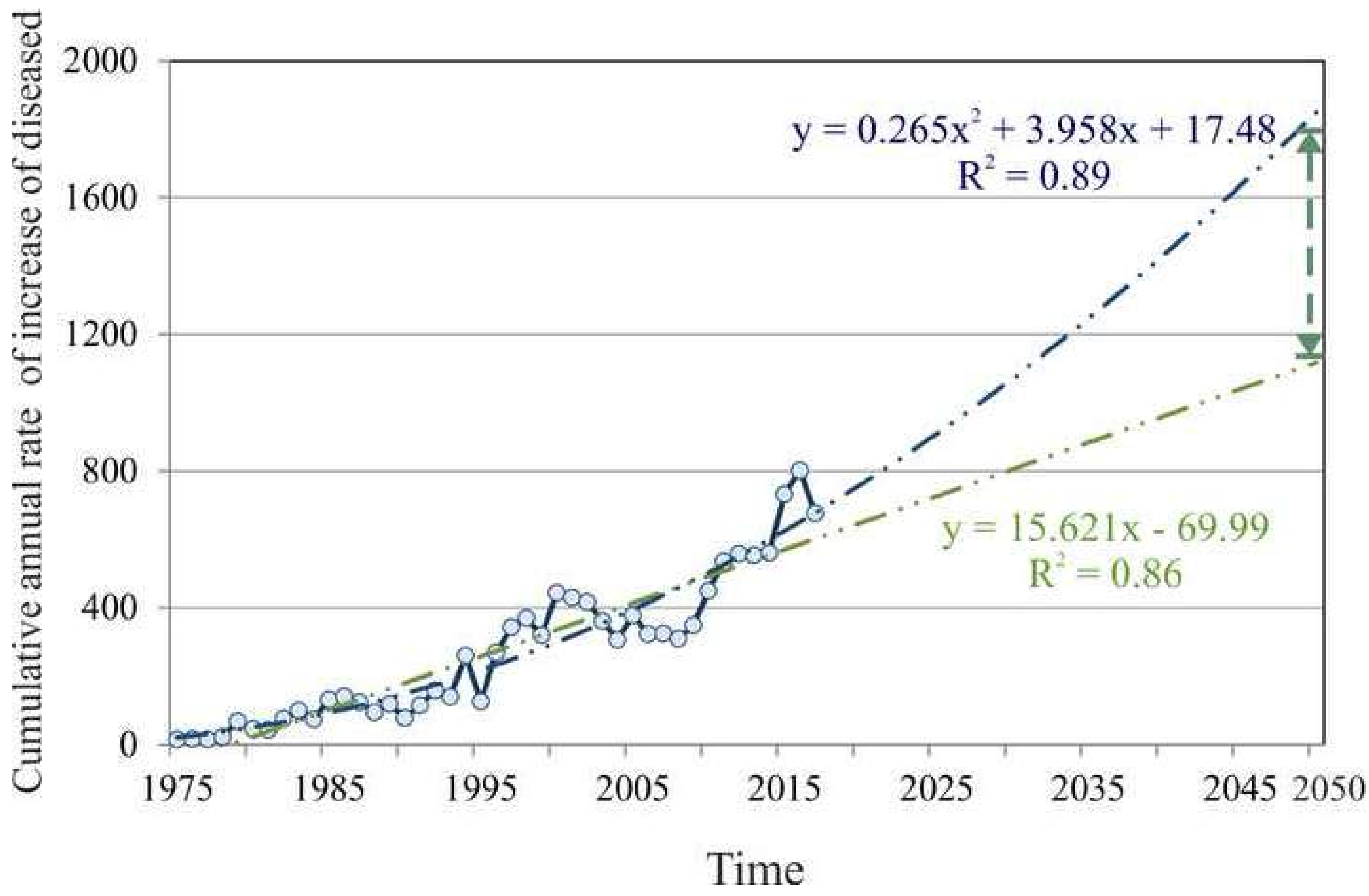


Figure 4 colour

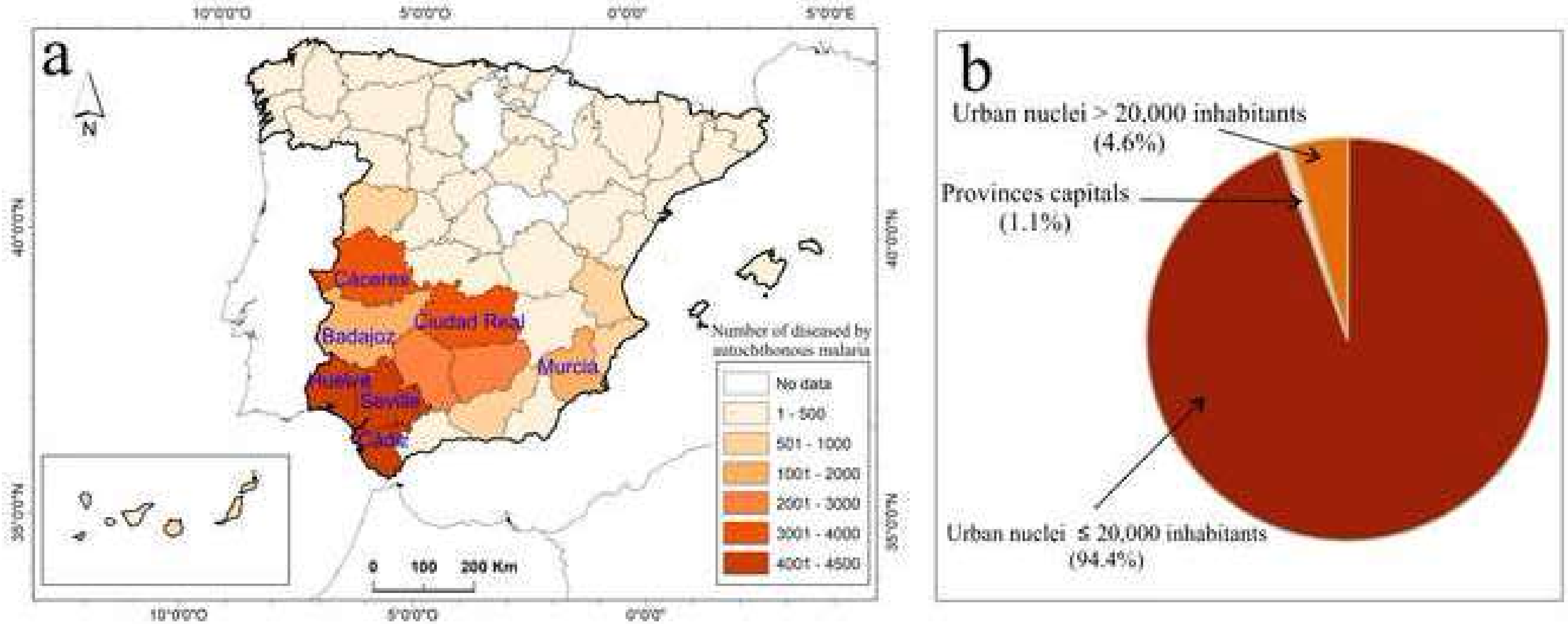
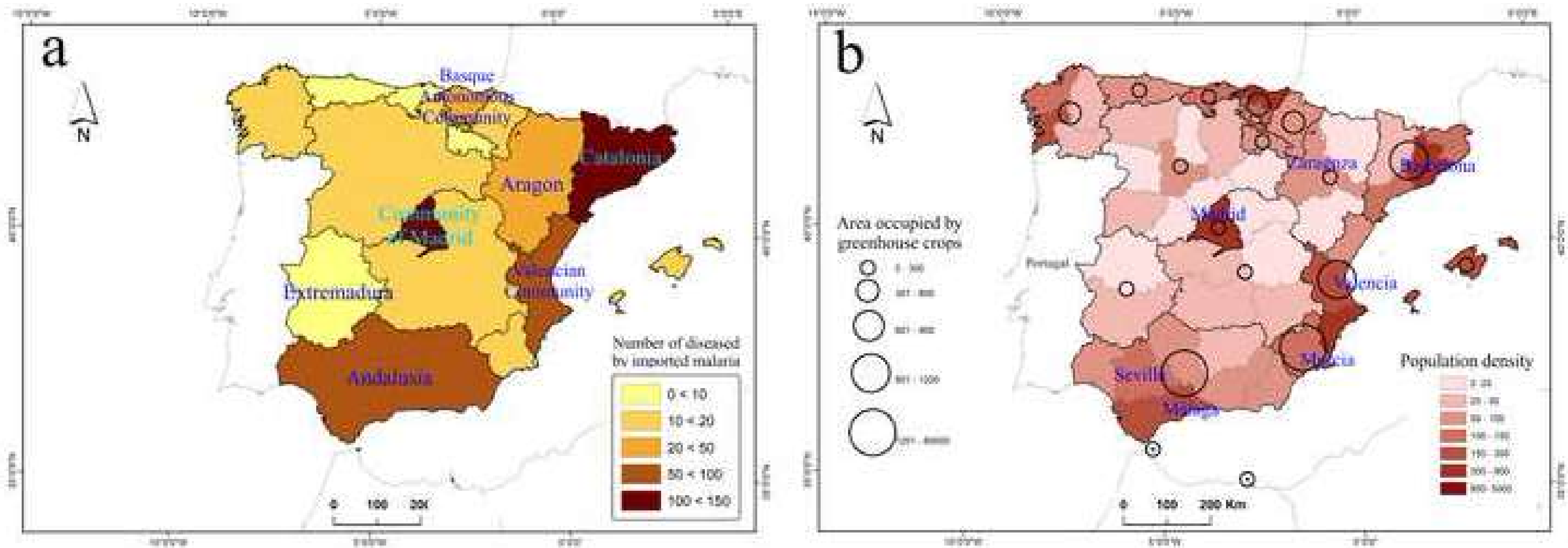
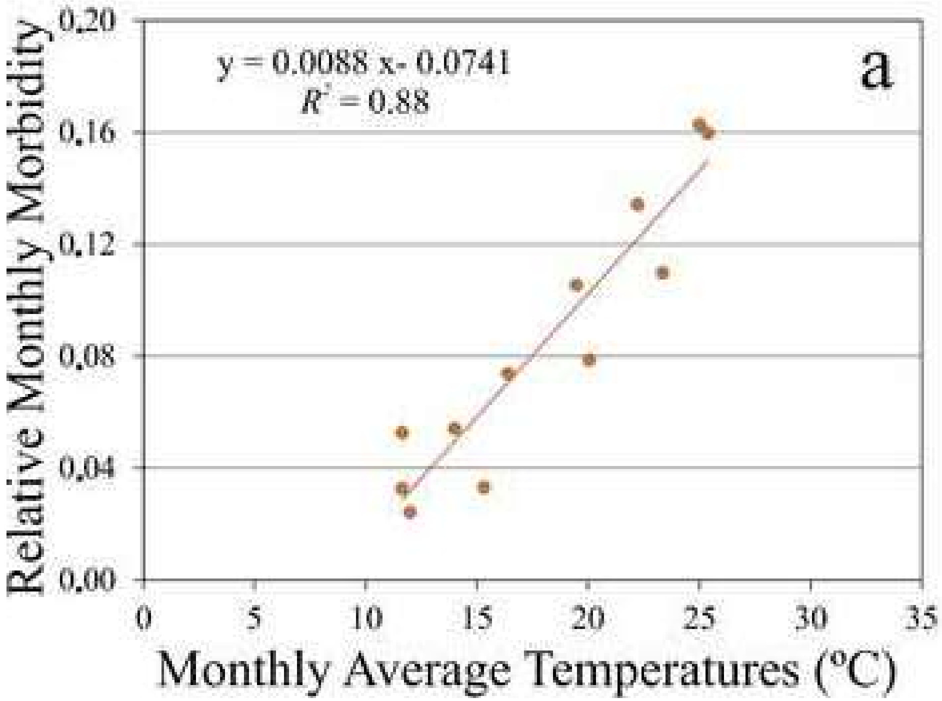
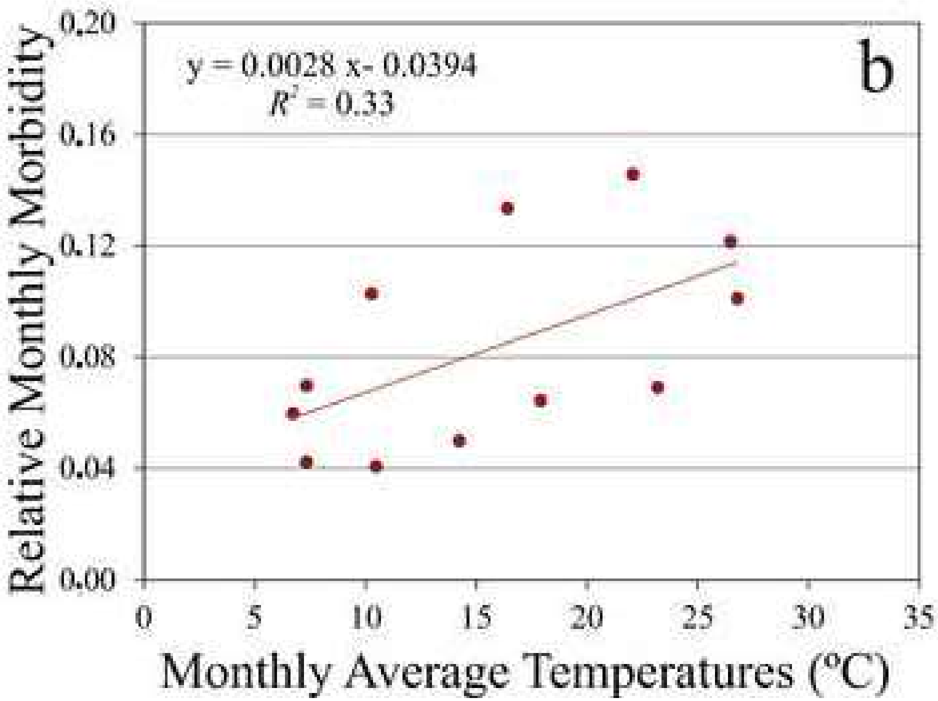
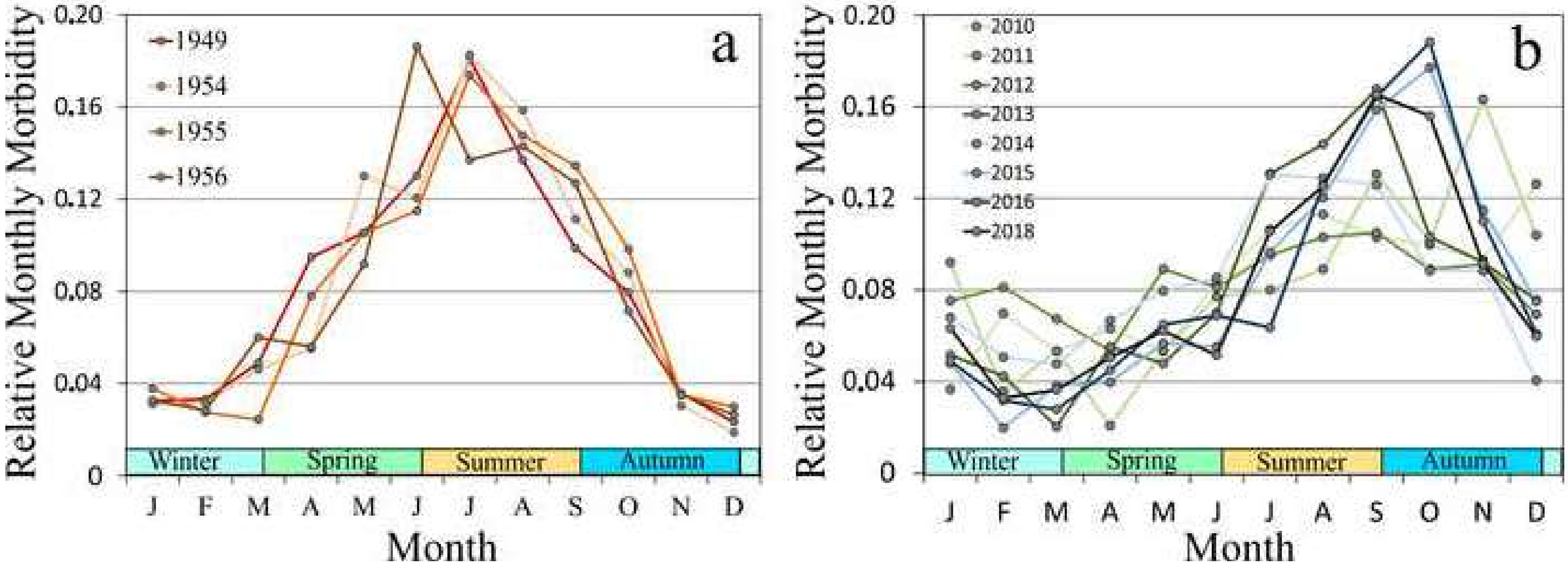


Figure 5 colour




y = 0.0088 x- 0.0741
R² = 0.88
a
Relative Monthly Morbidity
0,20
0,16
0,12
0,08
0,04
0,00
0
5
10
15
20
25
30
35
Monthly Average Temperatures (ºC)


y = 0.0028 x- 0.0394
R² = 0.33
b
Relative Monthly Morbidity
0,20
0,16
0,12
0,08
0,04
0,00
0
5
10
15
20
25
30
35
Monthly Average Temperatures (ºC)


a
Relative Monthly Morbidity
0.20
0.16
0.12
0.08
0.04
0
1949
1954
1955
1956
Winter
Spring
Summer
Autumn
J F M A M J J A S O N D
Month
b
Relative Monthly Morbidity
2010
2011
2012
2013
2014
2015
2016
2018
Month