atmosphere

Article

Spatiotemporal Distribution of Malaria in Spain in a Global Change Context

Arturo Sousa [1,*], Mónica Aguilar-Alba [2], Mark Vetter [3], Leoncio García-Barrón [4] and Julia Morales [1]

1 Department of Plant Biology and Ecology, Universidad de Sevilla, E-41012 Seville, Spain; jmorales@us.es
2 Department of Physical Geography and AGR, Universidad de Sevilla, E-41004 Seville, Spain; malba@us.es
3 Geovisualization, Würzburg University of Applied Sciences, Würzburg 97070, Germany; mark.vetter@fhws.de
4 Department of Applied Physics II, Universidad de Sevilla, E-41012 Seville, Spain; leoncio@us.es
* Correspondence: asousa@us.es; Tel.: +34-954-556-782

Received: 16 March 2020; Accepted: 30 March 2020; Published: 31 March 2020

Abstract: Malaria is one of the most cited vector-borne infectious diseases by climate change expert panels. Malaria vectors often need water sheets or wetlands to complete the disease life cycle. The current context of population mobility and global change requires detailed monitoring and surveillance of malaria in all countries. This study analysed the spatiotemporal distribution of death and illness cases caused by autochthonous and imported malaria in Spain during the 20th and 21st centuries using multidisciplinary sources, Geographic Information System (GIS) and geovisualisation. The results obtained reveal that, in the 20th and 21st centuries, malaria has not had a homogeneous spatial distribution. Between 1916 and 1930, 77% of deaths from autochthonous malaria were concentrated in only 20% of Spanish provinces; in 1932, 88% of patients treated in anti-malarial dispensaries were concentrated in these same provinces. These last data reveal the huge potential that anti-malarial dispensaries could have as a tool to reconstruct historical epidemiology. Spanish autochthonous malaria has presented epidemic upsurge episodes, especially those of 1917–1922 and 1939–1944, influenced by armed conflict, population movement and damaged health and hygiene conditions. Although meteorological variables have not played a key role in these epidemic episodes, they contributed by providing suitable conditions for their intensification. After the eradication of autochthonous malaria in 1961, imported malaria cases began to be detected in 1973, reaching more than 700 cases per year at the end of the second decade of the 21st century. Therefore, consistent and detailed historical studies are necessary to better understand the drivers that have led to the decline and elimination of malaria in Europe and other temperate countries.

Keywords: malaria; spatial analysis; temporal analysis; climate change; water bodies; wetlands; Geographic Information Systems (GIS); Spain

1. Introduction

Different vector-borne diseases have been associated with climate change, especially in the second half of the 20th century and early 21st century. For some of them, such as malaria, dengue, Rift Valley fever, Chikungunya virus and West Nile encephalitis, different species of mosquitoes act as vectors [1–3]. In this context, we use the term global change to refer to the complex of environmental changes that is occurring around the world as a result of human activities [4]. Therefore, global change includes not only climate change, but also changes in land use and habitats, in the vegetation cover, water cycle modification, biodiversity loss and the incursion of invasive species [5,6]. The changes resulting from globalisation, such as intercontinental air transport and global shipping, create new opportunities for invasive vectors and pathogens. Furthermore, changes in the distribution of vectors are being potentiated by climatic and environmental alterations [2], and thus meteorological variables are often used for modelling of these infectious diseases [7].

Among the infectious diseases transmitted by vectors, malaria shows a wide distribution, with one of the highest rates of morbidity and mortality worldwide. According to the World Health Organisation (WHO), in 2016, there were an estimated 216 million people infected and 445,000 killed by malaria [8]. Most of these cases (90%) were recorded in Africa, although the disease is still distributed among 91 countries all around the world. Therefore, malaria is a problem that is not confined to certain regions or countries; it is a global challenge for all of humanity in the 21st century. A good example of this is that, in 2016, the governments of countries with endemic malaria and their international partners (such as USA, Germany, etc.) invested approximately $2.7 billion for its eradication (most of these resources, around 74%, were invested in Africa) [8].

In Europe, the last endemic foci of autochthonous malaria were eradicated in the 1960s and 1970s [9]. In Spain, the last case of death by autochthonous malaria was recorded in 1959 and the last cases of the disease were reported in 1961, although it was in 1964 when it was declared officially eradicated by the WHO [10,11].

The origin of the vectors of the genus *Anopheles* and the protozoans of the genus *Plasmodium* that cause the disease allows classification of different forms of malaria. In the case of indigenous or autochthonous malaria, the disease is acquired through the sting of an infected mosquito in a country where malaria is present [10]. On the other hand, imported malaria refers to infected people who acquired the disease in endemic countries and are diagnosed or show symptoms in countries where the disease has been eradicated. These are the two most relevant types of malaria quantitatively, and thus the focus of the present study. Other types of malaria are induced malaria, airport or odyssean malaria and introduced malaria; the latter is acquired in countries where there is no malaria, through local mosquitoes that become infected with the parasite from a person or persons infected with imported malaria [1,10].

Recent studies on the whole of Europe [12] highlight an interest in historical reconstruction of the epidemiology of malaria, which can be used to differentiate the drivers of eradication of the disease. However, there are few studies with a thorough approach to the spatial distribution of malaria in the whole of Spain in the 20th and 21st centuries, with an even smaller number of studies using Geographic Information Systems (GISs) to produce a geospatial view of the disease [11]. A spatiotemporal approach can also help to better recognise the risk of re-emergence of induced malaria in temperate countries where it was eradicated, as well as more effective measures for the eradication of autochthonous malaria in those countries where it is still endemic.

Therefore, the aim of this study was to analyse the spatiotemporal distribution of the morbidity and mortality of malaria in Spain in the 20th and 21st centuries. From these results, we analysed the main epidemic outbreaks of autochthonous malaria, as well as the spatial distribution of the disease, by region and province. This may help to identify the main factors that explain the historically endemic areas of autochthonous malaria in Spain, as well as the main drivers of its eradication in the 20th century.

2. Materials and Methods

To achieve the objectives proposed in this study, we decided to use a multidisciplinary methodology, first from a temporal perspective, and then from a spatial perspective. This methodology includes the following sources of information: epidemiological data (from historical archives and databases with different spatial scales), regional data of unhealthy water bodies, records of the presence of malaria-carrier anophelines and data of antimalarial dispensaries.

2.1. Temporal Distribution of Malaria in Spain throughout the 20th and 21st Centuries

We used available data of autochthonous malaria from 1900 to 1964, when the disease was officially declared eradicated in Spain by the WHO. The data of imported malaria were recorded from 1973, when the first case was documented by the official statistical sources, until 2018, which is the last year of available data. This continuous recording of data was due to the fact that malaria is a notifiable infectious disease, since it poses a risk to public health [13]. These data are available in the historical archives of the annual reports of the Spanish Statistical Institute [14], which have been used by different authors in epidemiological studies [15–20].

For cases of autochthonous malaria, the archives have gathered annual reports or yearbooks, beginning in 1858 in compliance with the organic regulation of the general Statistical Commission of the Kingdom of Spain, and in a more thorough and regular manner from 1900 [11]. These data refer to the numbers of cases of infection and mortality, unhealthy water bodies, antimalarial dispensaries and positive cases of autochthonous malaria in antimalarial dispensaries. 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 1916–1930 (deceased) and 1949 and 1954–1961 (infected) [17]. The data related to the total number of people who died from malaria in Spain in the 20th century were also taken from SSIbase. The distribution of the Spanish regions and provinces can be found in Appendix A (Figures A1 and A2).

To analyse the provinces and regions of the whole of Spain where malaria had been more endemic in the early 20th century, we selected those provinces which included over 70% of the cases of death for the period 1916–1930. We calculated the percentage of decrease of deaths at the provincial scale, as well as the rate of decrease of deaths in each Spanish province with respect to the total for the entire country for that period. These data allowed us to analyse whether the distribution of the mortality of the disease was either homogeneous in Spain or concentrated in certain areas. The information generated was then completed with a map of the number of people infected by autochthonous malaria in Spain in the last years before it was totally eradicated. This allowed us to discuss the main factors that could explain the greater concentrations of cases of infection and death in different Spanish regions, and thus to understand which were the main drivers of autochthonous malaria in Spain in the 20th century.

The data of imported malaria were taken from SSIbase [14], from the epidemiological bulletins of the Carlos the Third Institute and Spanish National Epidemiology Surveillance Network [21] and the Sistema Básico de Vigilancia Comunitat Valenciana [22]. Epidemiological data show small differences depending on whether records from the national surveillance system or the hospital discharge database are used [23]. Therefore, other complementary sources with historical data for the 20th and 21st centuries were also consulted [24–26].

In addition to the temporal tendencies during the 20th and 21st centuries and the polynomial regression lines of the different types of malaria studied, we calculated the specific disparity index (I_d). This index has previously been used in different research areas, such as hydrology [27], limnology [18], erosivity [28] and climatology [29]. I_d provides information about the evolution of the irregularity of the variable, as it compares each element with the adjacent values of the series, i.e., the previous value and the following value [30]. For a series of N years, if v_n is the value of the variable of year n ($1 < n < N$), the calculation of I_{dn} is based on the deviations between the elements $\{v_{n-1}, v_n, v_{n+1}\}$ of the chronological series, with μ_n being the mean of the three consecutive values centred in n (Equation (1)):

$$I_{dn} = (\{[(v_n - v_{n-1})^2 + (v_{n+1} - v_n)^2]^{1/2}\} \times 1/2)/\mu_n \quad (1)$$

Therefore, this generates a new temporal series that allows detection of variability in the interannual behaviour of the total number of people infected and killed by malaria. That is, I_{dn} indicates the interannual variability in the records of cases of death and infection by autochthonous and imported malaria, and allows detection of significant changes in the temporal tendencies of consecutive years (e.g., at the beginning or end of an epidemic outbreak). These data were analysed according to economic tendencies and migration movements gathered in monographs of historical Spanish statistics of the 19th and 20th centuries [31].

2.2. Spatial Distribution of Malaria in Spain throughout the 20th Century

We used Geographical Information System (GIS) and/or geovisualisation tools to spatially represent different aspects related to the disease, such as the provincial distribution of the number of cases of infection and death, the presence of antimalarial dispensaries, the regional distribution of unhealthy water bodies, and the presence of records related to *Anopheles atroparvus* and/or *Anopheles labranchiae*. From the data of the years available in SSIBase [14], using GIS techniques, we generated maps, in absolute numbers, of the total cases of people killed and infected by autochthonous malaria in Spain. In the maps, which show the distribution of deaths and infections by malaria, we used the cartographic choropleth display method [32]. In this way, we can integrate and analyse sources of information, including the main drivers of the disease, for the whole of Spain. Different studies have used GIS tools to analyse the morbidity and/or mortality of malaria at a regional, national or global scale, as well as the main drivers of the disease [18,33–38].

The Appendix include the names of the provinces (see Figure A1) and the autonomous communities to which these provinces belong (see Figure A2), with the aim of making it easier for the reader to locate them on the maps presented in this study.

To locate the presence of the vectors that transmitted autochthonous malaria in Spain, we used the data available in the scientific literature, both from records of localities at the provincial scale and on maps, for *Anopheles atroparvus* and *Anopheles labranchiae* [39–43].

2.3. Antimalarial Dispensaries, Unhealthy Water Bodies and Vector-Borne Diseases

The antimalarial efforts in Spain were mainly focused on the activity of the dispensaries or laboratories that allowed the detection of malaria-infected people and provided free treatment, in addition to measures against mosquitoes and prophylactic campaigns [15,16]. The Spanish Institute of Statistics also offers, in SSIbase [14], historical information about these antimalarial dispensaries and the number of malaria patients attended to in each of them. There are available data from 1920, although incomplete and from different institutions. For the present study, we used only those data that appeared disaggregated at the local or provincial scale and that started partially in 1931 and were more homogeneous and continuous for 1932 and 1936–1949. These dispensaries were spatially geolocalised, and the data were grouped by province and region for each series of years with available data. This data source has been previously used by other authors to study, temporally and spatially, the effects of the Spanish Civil War and the malaria epidemic that took place after that conflict. The cartography produced from these data was synthesised in four maps for the following years: 1932 (the first year for which there are available data about antimalarial dispensaries), 1937 (with the war fronts of the Civil War of 1936–1939), 1941 (peak phase of the epidemic in the post-war period) and 1945 (the values of infection cases normalised after the end of the epidemic outbreak). The 1937 map gathers the approximate location of the war fronts of the two sides involved in the conflict. Likewise, we revised the data related to the location of troops and prisoner camps during the war and post-war periods as potential foci for malaria spread [44].

The presence/absence of antimalarial dispensaries and the number of infected people recorded in each of them were also compared with the presence of vectors and the surface area occupied by unhealthy water bodies. In this way, we were able to analyse the link between these aspects and the usefulness of antimalarial dispensaries as tools to better determine the spatial distribution of the disease in the past.

With respect to unhealthy water bodies, the available data for the whole of Spain were scarce and corresponded to the years 1915 and 1916, from reports of the health inspection carried out and published in 1915 and 1917 by the Spanish Office of Agriculture [45]. The map presents the index by applying different intensities in a colour ramp, using the choropleth display method, along with the location of all antimalarial dispensaries that existed in Spain in 1932.

3. Results and Discussion

In this study, we analysed the temporal evolution of autochthonous and imported malaria in Spain for the 20th and 21st centuries. Then, we carried out a spatial analysis (using GIS tools) to detect the main areas where autochthonous malaria was endemic in Spain. Lastly, we used the data of antimalarial dispensaries as a new tool to localise the main Spanish regions and provinces where the eradication of autochthonous malaria was more difficult to achieve, as well as the main environmental factors involved.

3.1. Temporal Distribution of Malaria in Spain throughout the 20th and 21st Centuries

Since the factors that influence the prevalence of autochthonous and imported malaria are very different, they were analysed separately. Moreover, from the quantitative perspective, the numbers of infection cases of the two types of malaria were very different. Furthermore, the cases of autochthonous malaria are all from the 20th century (first analysis), and the cases of imported malaria occurred in the late 20th and early 21st century (second analysis).

3.1.1. Autochthonous Malaria

Figure 1a represents the evolution of the absolute number of people who died from autochthonous malaria in Spain with respect to the absolute number of deaths in the 20th century. To compare the two variables in this graph, total mortality is represented as a quotient of 100. These tendencies are complemented in Figure 1b, which shows the evolution of the specific disparity of the number of deaths by autochthonous malaria for that period of time. That is, Figure 1a shows the general tendencies and Figure 1b shows the variability of malaria mortality as a function of time (in years).

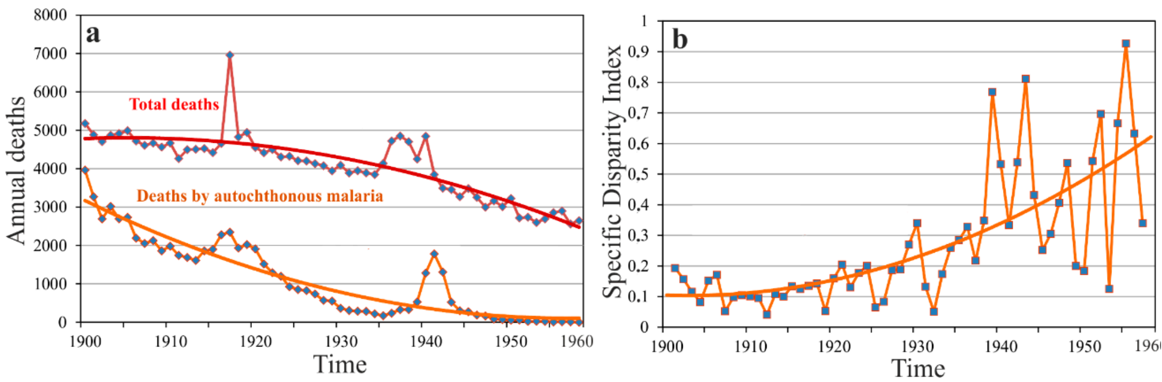

Figure 1. (**a**) Evolution of total number of deaths by autochthonous malaria with respect to absolute number of deaths in Spain in the 20th century. Total number of deaths is represented as a quotient of 100, to allow a comparison between tendencies. (**b**) Evolution of specific disparity index of mortality by autochthonous malaria in Spain for the 20th century.

When we compared the evolution of the total number of deaths for all causes with the number of deaths by autochthonous malaria, uncommon tendency patterns were observed. This is very clear when comparing the two polynomial tendency lines (Figure 1a). Both tendency lines fit quadratic functions, as can be observed in Equation (2), where M_m is the number of deaths by autochthonous malaria:

$$M_m = 0.83 \times n^2 + 9.8 \times n + 4475 \quad (2)$$

with an explained variance $R^2 = 0.85$, where n represents the lapsed years, and

$$M_T = 0.95 \times n^2 - 110.1 \times n + 3278 \quad (3)$$

with an explained variance $R^2 = 0.73$ in Equation (3) for total deaths M_T.

In the early 20th century, a sharp drop in the number of deaths by malaria is detected, which becomes progressively milder until the complete eradication of endemic malaria. However, the decrease of total deaths, in absolute numbers, is very low in the early 20th century and becomes sharper from the 1940s. That is, total deaths show a more convex reduction slope, probably due to the increase in total mortality of different causes during the Spanish Civil War (1936–1939). In fact, in only 10 years (1935–1945), the total number of annual deaths decreased from 384,567 to 327,045, a reduction of 14.9%. On the other hand, the deaths by malaria show a more concave reduction slope.

The specific disparity index d_n measures the consistency of the tendency of annual mortality values with respect to the previous year and the following year, thus it represents the irregularity of high-frequency behaviour along time. Figure 1b shows, in the first three decades of the 20th century, the relative stability ($d_n < 0.2$) of the rate of interannual decrease in deaths by malaria, which indicates similar interannual values in consecutive years. From 1940, when the absolute value of deaths had already decreased, the average disparity increased ($d_n = 0.5$), and with a greater oscillation range. In the first decades of the 20th century the quadratic adjustment (Figure 1b) highlights the small oscillations of the mortality series regarding to the adjustment line. However, from 1940 onwards the interannual mortality trend increases with large deviations between consecutive years. This increase in the variability of the number of deaths by malaria between consecutive years can be due to several factors, such as local or regional campaigns to eradicate the disease and epidemic episodes in the early 1940s. Moreover, as the distribution of deaths narrows down to certain endemic areas, the interannual patterns can show greater oscillation due to the influence of local factors, such as the presence of unhealthy water bodies or different vectors. The progressive decrease in the number of cases is also an influencing factor, since the small absolute interannual variations are sharper in relative terms.

When comparing the evolution of the number of deaths by malaria with the total number of deaths from the early 20th century, we observed different epidemic episodes or peaks which did not always overlap in time (Figure 1a). The first peak appeared in 1918, coinciding with the end of the First World War (1914–1918). In that year, there was a very sharp increase in total mortality, as well as an increase in the number of deaths by malaria, which extended to 1922. In the case of total mortality, it is important to remember that, during 1918–1919, Spain was one of the most affected countries by the wrongly called "Spanish influenza" pandemic [20,46]. In 1918, the total number of deaths by influenza was estimated to be at least 147,114 people [46]. According to the archive data of SSIbase, the total number of deaths in Spain increased from 465,722 in 1916 to 695,758 in 1918 (an increase of 230,036 deaths between 1917 and 1918, in comparison with an increase of 24,049 deaths between 1916 and 1917). It is worth highlighting the temporal overlap of the two peaks of death by influenza and by autochthonous malaria, two diseases characterised by febrile peaks.

A second peak overlaps temporally with the Spanish Civil War (1936–1939). Even with the imprecision of counting the deaths among combatants and the civil population, a logical increase in total mortality is detected between 1936 and 1940. On the other hand, the number of deaths by malaria increased in the post-war period (1940–1944), with a gradual increase from 1936 (170), 1937 (237), 1938 (329), 1939 (334), 1940 (530) and 1941 (1283), until reaching a maximum in 1942 (1781 deaths by malaria). Different authors [15,16,47] have associated this aggravation with population displacement, hunger, the scarcity of antimalarial medicines and the proliferation of anophelines due to the abandonment of antimalarial campaigns. The values of 1935, i.e., before the civil war, are observed again only from 1947.

We compared the data of deaths during the epidemic peaks of autochthonous malaria with the main tendencies of the climatic variables. To that end, we analysed the tendencies of annual and seasonal rainfall and maximum and minimum monthly and seasonal temperatures (especially in spring and summer) in the most endemic areas of Southwestern Spain, such as Extremadura and Western

Andalusia [45]. To analyse the effect of climatic variables on these epidemic peaks of autochthonous malaria, we used the meteorological records of SW Spain. Although this aspect will require future studies with more detailed analyses, we did not detect a cause–effect relationship between the climatic variables and the peaks of deaths by autochthonous malaria in Spain in the 20th century. However, we did observe that for the number of deaths to increase substantially, there must be warm and moderately rainy spring–summer periods with respect to the interannual average. This is reasonably related to the viability and reproduction capacity of the species of anophelines and *Plasmodium* involved either directly [48,49] or from the water sheets and unhealthy water bodies they require to complete their biological cycle [3,17]. The average daily temperature determines whether the extrinsic life cycle of the parasite in anophelines can take place [9]. Over a sustained temperature of 38 °C, the parasite is not transmitted [10], since the optimal temperature range for development of the parasite *Plasmodium vivax* inside the mosquito is 16–33 °C [50]. A recent study [51] shows the covariance of monthly morbidity of autochthonous malaria and monthly thermal variables ($R^2 > 0.84$) in Spain. To assess the importance of the thermal variables to the morbidity of malaria in Spain, it must be taken into account that the present study used the data of 1949–1961, when the hygienic–sanitary and socioeconomic conditions had radically improved in Spain, right before the complete eradication of autochthonous malaria.

These results are also in line with broader studies carried out all over Europe. At the European scale, the main factors involved in the eradication of autochthonous malaria were socioeconomic and related to the use of the land, although many other factors may have also played a relevant role. These factors include the strengthening of surveillance and healthcare systems, changing lifestyles, the construction of homes and the presence of different species of anophelines [12].

If we consider the two main peaks of deaths by malaria in Spain in the 20th century, it can be observed in the meteorological variables of 1918, and especially in 1938 and 1943, that spring and early summer were rainy and warm. That is, seasonal climatic conditions contributed to the increased disease spread in the summer months, although they were not the main driver. In the entire European context, high temperatures, increased precipitation and fewer frost days have historically favoured the transmission of malaria [12].

On the other hand, there are no detailed spatial studies with GIS techniques that allow a discussion of the spread of the outbreak associated with the post-war period in Spain. The scarcity of complete provincial statistical data for this period hinders the spatiotemporal analysis of this outbreak. Therefore, this topic was later addressed using the available data of antimalarial dispensaries.

Up to this point, we have only presented an analysis of the data related to the number of deaths. For the number of people infected, we have only incomplete records in the historical archives of the 20th century (specifically for the period 1949–1961). Equation (4) relates the number of annual cases of sick people to the number of deaths by malaria in the period 1949–1958:

$$D_m = 370 \times M_m - 4028 \quad (4)$$

where D_m is the number of people infected with autochthonous malaria and M_m is the number of deaths by malaria. The coefficient of determination between these two variables for the period 1949–1958 is $R^2 = 0.86$, which indicates that the regression of autochthonous malaria is constant for this entire period, allowing us to estimate that there was one case of death per 356 cases of sickness. It is important to take into account that this covariance cannot be linearly extrapolated to periods before the 20th century, when the rate of mortality was greater with respect to an equivalent morbidity. Although we do not have long series of data that allow an accurate reconstruction of the situation in the early 20th century, the regional data of the inventories of SSIbase [14] related to 1913 and 1916 provide an approximate idea. Between 1913 and 1916, there was an average rate of 20.6 deaths per 356 cases of illness, with a coefficient of determination $R^2 = 0.79$ (up to 0.90 only for 1913). With respect to the average in the whole of Spain, there was a remarkable mortality rate in the region of Extremadura and a lower mortality rate in the region of Levante for an equivalent morbidity [11].

These results, as well as previous works [11,45], indicate that the number of deaths does not show a homogeneous distribution in the country, but it is concentrated in certain regions, and within these in certain provinces. In this sense, using the mortality data at the provincial scale between 1916 and 1930, we can conclude that 77% of deaths by autochthonous malaria were concentrated in only 20% of the Spanish provinces. That is, mortality by malaria was concentrated in only 10 of the 50 Spanish provinces in the early 20th century. Table 1 shows the annual proportion of deaths by malaria in these 10 provinces with higher mortality (>4% with respect to the national total).

Table 1. Concentration of deaths by autochthonous malaria in 10 Spanish provinces with higher mortality in the period 1916–1930.

Year	Absolute Number of Deaths in 10 Most Endemic Provinces	Absolute Number of Deaths in All of Spain	Proportion of Absolute Number of Deaths in Most Endemic Provinces with Respect to the Total
1916	1547	1899	0.81
1917	1795	2279	0.79
1918	1846	2354	0.78
1919	1485	1933	0.77
1919	1485	1935	0.77
1920	1570	2044	0.77
1921	1409	1918	0.73
1922	1148	1527	0.75
1923	966	1291	0.75
1924	924	1195	0.77
1925	693	925	0.75
1926	661	839	0.79
1927	630	832	0.76
1928	558	736	0.76
1929	424	567	0.75
1930	405	556	0.73
Total	17,546	22,830	Average = 0.77

To obtain a complete view of the evolution of malaria in Spain in the 20th century, it is necessary to know what happened from 1964, when autochthonous malaria was officially declared eradicated [10]. That is, it is essential to know whether there have been other types of malaria associated with the greater movement of people and goods in the context of global change characteristic of the 21st century.

3.1.2. Imported Malaria

The last case of death by malaria in Spain occurred in 1959, and the last 24 cases of people infected with autochthonous malaria were recorded in 1961 [17], in the provinces of Huelva, Salamanca, Toledo and especially Cáceres (21 sick people). Between 1962 and 1972, we found no record of morbidity. The first cases were recorded in 1973, although this study only shows the cases from 1975. From that date, the number of cases recorded has made malaria the most frequently imported disease in Spain, mainly by travellers and migrants [23], among whom about 700 imported malaria cases are reported annually. Figure 2a represents the general tendencies of imported malaria from 1975 to 2018, and Figure 2b shows the specific disparity index of imported malaria for that period.

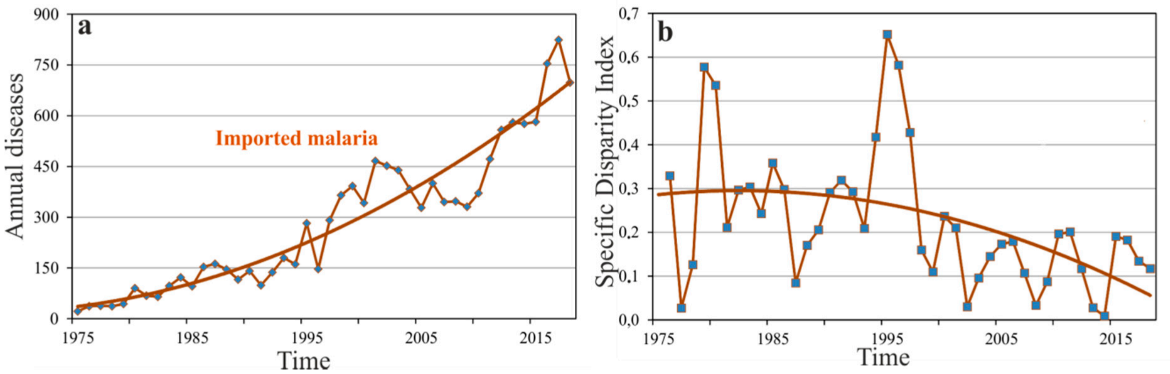

Figure 2. Evolution of: (**a**) absolute number of people infected with imported malaria; and (**b**) specific disparity index of morbidity by imported malaria in Spain from 1975 to 2018.

Figure 2a shows a significant quadratic tendency in terms of the number of cases of imported malaria from the late 20th century to the early 21st century (D_I).

$$D_I = 0.26 \times n^2 + 3.74 \times n + 32.2 \text{ with } R^2 = 0.90 \quad (5)$$

In addition to this increase in the number of infected people (Figure 2a), two periods are detected with a progressive increase in morbidity (1996–2001 and 2009–2017), and an intermediate period (2001–2009) in which the number of cases recorded decreases or becomes stable. This decline was also observed in some European countries where a decrease in imported malaria was detected, probably due to controls in endemic countries, an increase in malaria-free countries, or perhaps low reporting of cases [52].

Figure 2b represents the constancy of the tendency of annual values of morbidity by imported malaria with respect to the previous year and the following year through the specific disparity index (d_n). Therefore, it shows the irregularity of high-frequency behaviour along time, i.e., the relative increase of year n with respect to the preceding year. Thus, the deceleration observed in Figure 2a from the early 21st century is clearer. In fact, from 2001, the specific disparity was $d_n < 0.21$, although 1979 and 2007 also stand out, with a variability of recorded cases between successive years of $d_n > 0.58$. It is worth highlighting that the specific disparity index of mortality increases as the disease approaches its date of eradication (Figure 1b), whereas in the 21st century the specific disparity (d_n) of the number of people infected with imported malaria tends to stabilise (Figure 1b).

It would be interesting to analyse whether there have been changes in the national system of records or in administrative aspects that can explain these fluctuations. In this respect, a very recent study [23] shows that the compulsory reported disease records indicate some discrepancies with hospital records, as is the case in other countries. Moreover, it is important to consider that hospital records may be overvalued due to readmissions and/or erroneous classification in certain years [23]. The global analysis of the evolution of the migration flows and economic tendencies, in both the period of increased national productivity for real estate development (1986–1992) and the more recent economic crisis of 2008–2014, did not directly show any clear relationship that links migratory or touristic movements with endemic countries. However, this connection seems obvious in the context of global change.

In Spain, imported malaria cases generally correspond to immigrants, immigrants who return to visit their friends and relatives and international travellers returning from endemic areas. These areas are mainly in sub-Saharan Africa, particularly Equatorial Guinea, a former Spanish colony [23,53,54]. Other countries, such as France, Italy and the United Kingdom, have also seen a greater number of imported malaria cases from former colonies with which they have historical and economic ties [55,56]. Among international travellers, some cases are also associated with travel to Latin America and Asia [57].

Most studies have identified *Plasmodium falciparum* as the predominant species responsible for imported malaria, not only in Spain [23,57,58], but also in other countries such as the United States [59], the United Kingdom [60] and France [61]. It must be taken into account that not many of these travellers and immigrants carry out correct anti-malarial prophylaxis [62], so informing people of the need to take appropriate preventive measures before travelling to endemic countries is essential.

Future research could focus on the link between endemic areas and migratory and touristic flows, with the aim of verifying the relevance of this factor in cases of imported malaria, since they probably are concentrated in certain countries. Another interesting aspect to develop in the future would be the spatial distribution of these cases among large urban nuclei or transit points (such as airports and main transportation routes), since previous studies showed that autochthonous malaria was strongly linked to rural areas. Thus, in 1955, 2514 cases of autochthonous malaria were reported, of which 93% belonged to municipalities of fewer than 20,000 inhabitants and only 0.8% to capitals of provinces [11]. On the other hand, between 1996 and 1999, the cases of imported malaria were concentrated in the two regions with the two most populated cities of Spain: Madrid and Catalonia [21]. In this way, a recent study [58] deduced that the epidemiological profile of malaria cases corresponded to a young person from sub-Saharan Africa residing in an urban area. Therefore, the markedly rural distribution of malaria in Spain in the first two-thirds of the 20th century appears to be related to the proximity of wetlands and other flooded areas, which acted as reservoirs for the vector of the disease. However, in the late 20th century and early 21st century, such distribution appears to be rather linked to large urban nuclei and international transportation routes.

3.2. Spatial Distribution of Malaria in Spain throughout the 20th Century

Figure 3a,b shows the spatial distribution of people infected with autochthonous malaria in the whole of Spain in 1949 and 1959, respectively, when there was a drastic regression of the disease until the last cases officially recorded in 1961. In 1949 (Figure 3a), sick people were mainly concentrated in the southwest, with over 2500 cases recorded in five provinces, especially Western Andalusia (Huelva, Cádiz and Seville), which had more than 4000 cases each, followed by Murcia with over 1600 infected people recorded in 1949. On the other hand, in 1959 (Figure 3b), the disease appeared in only some provinces and in very small numbers (Figure 3b).

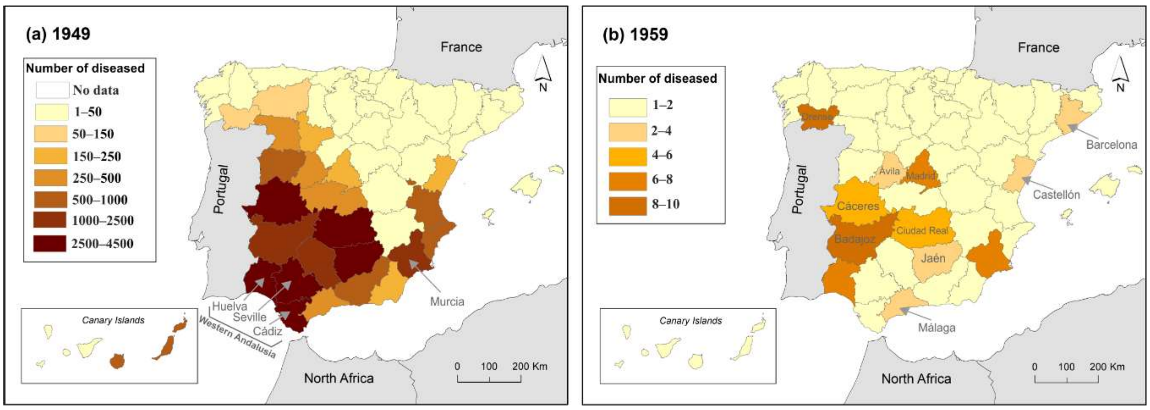

Figure 3. Spatial distribution of total number of people infected with autochthonous malaria in each Spanish province in: (**a**) 1949; and (**b**) 1959.

The next question is whether the spatial distribution of people infected with autochthonous malaria in Spain (Figure 3) was equivalent to the spatial distribution of deaths (Figure 4). Figure 4a shows a comparison, through a scale of colours, of the average percentage of deaths in each province with respect to the national total (1916–1930). For the same period, Figure 4b establishes the regression intervals of the number of deaths as a function of the values of the coefficient of the tendency line (*m*): low (−2.5 to −4.5), medium (−6 to −9.77), high (−16.66) and very high (−31.22). To this end, we selected the 10 provinces that had the highest concentration of deaths (see Table 1) and are the most relevant, since they include 75% of all cases of death from malaria in the whole of Spain.

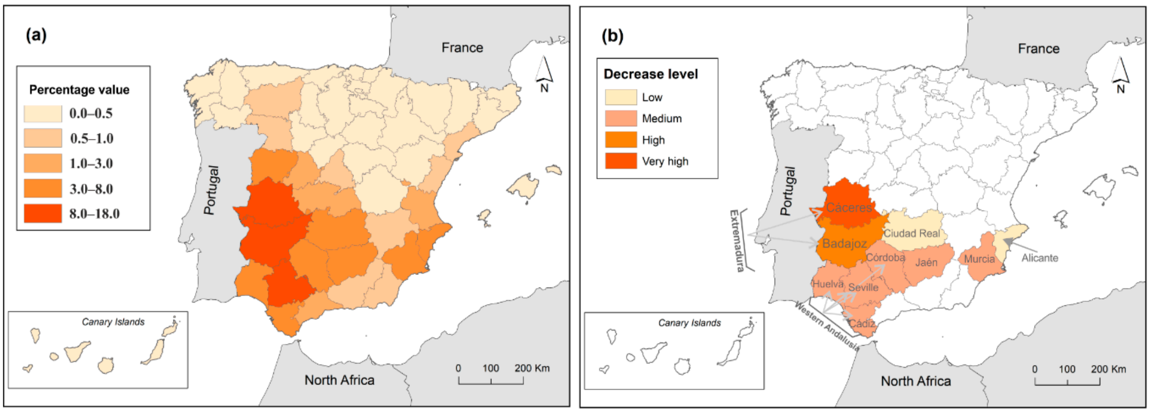

Figure 4. (**a**) Percentage of deaths in each Spanish province with respect to national total for 1916–1930. (**b**) Provincial rate of regression of number of deaths in each Spanish province with respect to the total in the whole of Spain.

Figure 4a shows a pattern of the distribution of deaths comparable to the spatial distribution of infected people (Figure 3). Thus, the regions with a higher concentration of deaths by malaria were Extremadura, Western Andalusia and Murcia, in that order. Figure 4b shows that these three regions improved their hygienic–sanitary conditions at a much greater rate than the rest of the regions, and they had a more drastic decrease in mortality by autochthonous malaria in the early 20th century. This seems explainable, since these are the regions with a greater margin of improvement in the desiccation of unhealthy water bodies and the development of other hygienic–sanitary measures, even though, decades later, they continued to have the highest concentration of sick people (see Figure 3). Likewise, the regression of the disease is more pronounced in these provinces than in the rest of the country. The provincial calculation of the linear coefficient of tendency (m) shows that the interannual decrease was very intense in Extremadura: $m = -31.2$ in Cáceres and $m = -16.6$ in Badajoz (precisely the most affected provinces during 1916–1930). However, the region of Levante shows a slight increase until 1922, before the disease began to decrease.

This different behaviour in the rate of regression of mortality at the regional scale could be related to the drivers that regulated the existence of the main foci of malaria. That is, in the region of Extremadura, some drivers may have been different from those of Western Andalusia or Murcia. Previous studies related the prevalence and mortality of malaria in Extremadura, with respect to the Spanish average, to local socioeconomic conditions [11]. Other authors have related the uniformity of the patterns of different provinces of Western Andalusia to a broad area of unhealthy water bodies [45]. In the case of Murcia and Alicante, apart from the presence of unhealthy water bodies, this has been related to the presence of a more anthropophilic vector (*Anopheles labranchiae*) along with *A. atroparvus* [40].

Therefore, we can globally assert that morbidity and mortality by autochthonous malaria were concentrated in certain Spanish regions and provinces. Moreover, during the entire process of eradication, the regions with the most cases were the same throughout the 20th century.

It also seems logical that these regions had the greatest amounts of resources and specialised personnel to fight malaria, and thus the most antimalarial dispensaries. If this can be confirmed, the information of antimalarial dispensaries could help us know with more detail the evolution and spatial distribution of malaria in the 20th century.

3.3. Antimalarial Dispensaries as a Tool for the Spatial Study of Malaria

3.3.1. Antimalarial Dispensaries

Table 2 shows the regional distribution of antimalarial dispensaries in Spain in 1932. Again, most of them (12) were located in Extremadura, with 75% specifically in the province of Badajoz, followed by Western Andalusia, Levante and Murcia (with four dispensaries in Murcia and one in Alicante). Regarding the number of sick people recorded (malaria-positive), Extremadura, Western Andalusia and Levante-Murcia stand out again, in that order.

Table 2. Distribution of antimalarial dispensaries in Spanish regions in 1932.

Region	Total Number of Dispensaries	Absolute Number of Infected People in Dispensaries *	Percentage of Infected People by Region (%) *
Levante and Murcia	5	4381	18.5
Castilla la Vieja	2	170	0.7
Extremadura	12	8662	36.7
Eastern Andalusia	3	624	2.6
Western Andalusia	9	7649	32.4
La Mancha	2	567	2.4
Leonesa	2	281	1.2
Catalonia	1	283	1.2
Castilla la Nueva	1	1007	4.3
Total	37	23,624	100

* The dispensary of Camporredondo was excluded for this calculation (Jaén, Eastern Andalusia).

In the province of Jaén (Eastern Andalusia), the antimalarial service was initially established in the dispensary of Camporredondo. This dispensary served up to 35 localities of the upper Guadalquivir River basin [16]. According to the data of SSIbase [14], in 1932, this dispensary attended to a total of 12,263 infected people, i.e., approximately one-third of all sick people recorded in all Spanish antimalarial dispensaries for that year. Therefore, this was not included in the morbidity data of Table 2, since it would distort the rest of the regional data. From 1930, the number of dispensaries increased in localities around the dispensary of Camporredondo, such as Linares, Villacarrillo, Castellar, Andújar and Puerta de Segura. At the same time, the Guadalquivir Hydrographic Confederation and the mining companies of the area also started developing activities against malaria for their own employees.

The results of Table 2 show that, in general, the antimalarial dispensaries were located in areas with greater concentrations of morbidity and mortality, which is in line with the results shown in Figures 3 and 4. The number of dispensaries can also be related to the number of people assisted by them in each region. The obtained results show that $R^2 = 0.94$, although the sample size was small. In the same analysis at the provincial scale, the sample size was larger ($n = 16$), and there was still a high correlation between the two variables, with $R^2 = 0.85$. That is, the number of dispensaries and their locations serve as good indicators of the endemicity of the disease. The following sections show the possible spatial links between the locations of these antimalarial dispensaries and potential drivers of the disease, such as the presence of unhealthy water bodies or the existence of some species of vectors, which historically transmitted malaria in Spain.

3.3.2. Antimalarial Dispensaries and Unhealthy Water Bodies

Figure 5 shows the locations and numbers of infected people recorded by antimalarial dispensaries in 1932 along with the surface occupied by unhealthy water bodies in each region (ha).

In Figure 5, the circle size represents the number of sick people assisted locally by each dispensary in 1932. As can be observed in the legend of this figure, the circle size does not have a direct proportional relationship with the number of infected people due to the graphic limitations that such an association would imply. The dispensary of Camporredondo is represented by a different symbol, since it had a much higher concentration of assisted people than the rest of the centres (over 12,000 positive cases in 1932 alone). The data related to the surface occupied by unhealthy water bodies are only available in the yearbooks of 1913 and 1917 of SSIbase [14]. This surface refers to areas of flooded terrain that needed to be disinfected or desiccated to prevent them from becoming malaria foci due to the development of anophelines in 1916 [11]. Considering that many species of anophelines need water bodies to complete their biological cycle, a legal regulation was created in Spain to desiccate these wetlands, which is known as the Cambó Law of 24 July 1918, along with other regulations.

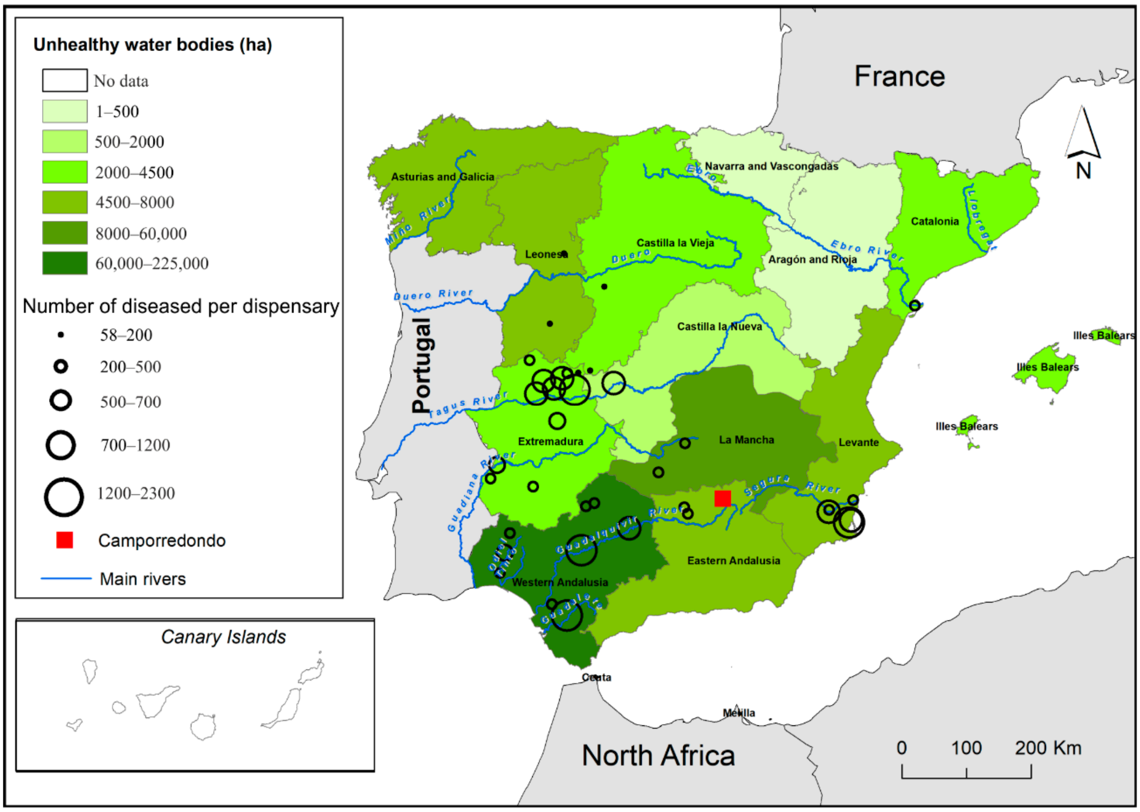

Figure 5. Regional surface occupied by unhealthy water bodies in the early 20th century in Spain and locations and numbers of infected people recorded by Spanish antimalarial dispensaries in 1932.

Unhealthy water bodies occupy a wide area in Western Andalusia due to the great extension of Atlantic marshes, especially those of the Guadalquivir River, in the early 20th century (see Figure 5). The rivers are another factor to take into account, since they can generate favourable environments for the reproduction of vectors. The antimalarial dispensaries were concentrated in Northern Extremadura, near the Tajo River, and linked to low hygienic–sanitary or socioeconomic conditions compared to the rest of the Spanish regions. There was also a remarkable concentration of centres and infected people in Murcia, near Mar Menor and the Segura River. In Western Andalusia, the dispensaries also treated many sick people, between 1200 and 2300, in localities near the Guadalquivir River and its marshes or, in the case of Huelva (southwest), near the water courses and marshes of the Odiel and Tinto Rivers.

Up to this point, we have presented the regional distribution of antimalarial dispensaries (Table 2) and their spatial localisation (Figure 5). However, in the provinces of the same region, the distribution of malaria was not necessarily homogeneous. That is, it could be more concentrated in some provinces than others within the same region. Knowing this information allows us to provide details on the localisation of the main foci of endemic malaria in Spain throughout the 20th century. Figure 6 shows the distribution, from higher to lower, of the provincial percentage of people infected with malaria recorded in 1932, in a sector diagram.

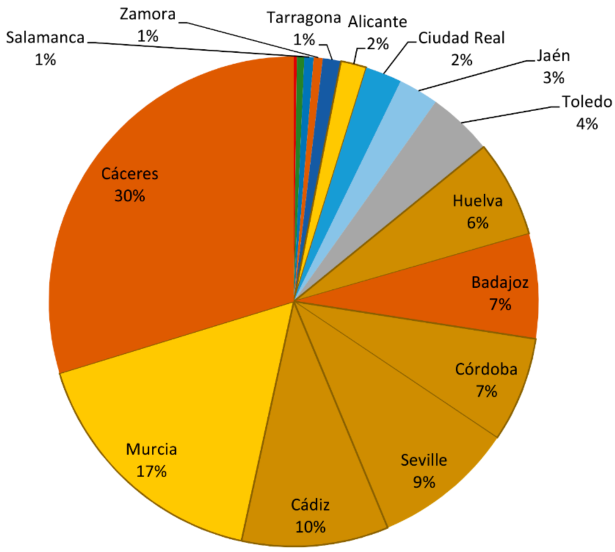

Figure 6. Provincial distribution (%) of cases recorded as positive for autochthonous malaria by Spanish antimalarial dispensaries in 1932. Provinces of the regions of Extremadura (Cáceres and Badajoz) are shown in the same colour, as are those of Western Andalusia (Cádiz, Seville, Córdoba and Huelva).

At the provincial scale, Figure 6 shows that, within these main regions (Extremadura, Murcia and Western Andalusia), the provinces with the highest percentage of morbidity are Cáceres (almost one-third of the cases), Murcia (17%), the provinces of Western Andalusia (Cádiz, Seville, Córdoba and Huelva), and the second province of Extremadura (Badajoz). Other provinces have very little representation: Toledo, Jaén, Ciudad Real, Alicante and Tarragona, between 4.3 and 1.2%. The rest of the provinces (Zamora, Salamanca, Ávila and Valladolid) are below 1% of the total.

Another aspect to analyse is whether this regional distribution of the morbidity of autochthonous malaria was related to the distribution of vectors that transmitted the disease in Spain. As in other European countries, the study of mosquitoes in Spain in the first half of the 20th century was related to the fight against malaria, which led in 1920 to the creation of the central Antimalarial Commission [42].

3.3.3. Distribution of Malaria Vectors and Unhealthy Water Bodies

Among the approximately 80 species of the genus *Anopheles* reported in Europe [42], 14 have been described in Spain as potential vectors of malaria [3], with the main vector being *Anopheles atroparvus* (in a large part of Europe). On the other hand, *A. labranchiae* is a North African species abundant in wide areas in the north and west of the Atlas Mountains that managed to colonise some regions of Southern Europe [42]. Historically, both species have been potential transmitters of malaria in Spain. Figure 7 shows the distribution of localities where the presence of *Anopheles atroparvus* and *Anopheles labranchiae* was recorded.

Figure 7 shows numerous localities near the main rivers and marshes with records of vectors, such as the Guadalquivir River basin and its marshes, the Segura River, the Ebro River mouth (Catalonia) and the Tajo River basin in the north of Extremadura. The concentration in the north of Extremadura also stands out with respect to the coincidence of localities with the dense network of rivers and tributaries in that area. When comparing Figures 5 and 7, we can see that the regions with more unhealthy water bodies, such as Western Andalusia, coincide with more localities with records of *Anopheles atroparvus* (e.g., the Guadalquivir River basin and the marshes of the Tinto and Odiel Rivers). On the other hand, the provinces of Murcia and Alicante stand out for the presence of both *Anopheles labranchiae* and *A. atroparvus* in the Segura River basin. These two regions also had many antimalarial dispensaries (Figure 5) and infected people (Figure 6), in addition to the north of Extremadura, which had one of the lowest socioeconomic levels of Spain in the early 20th century.

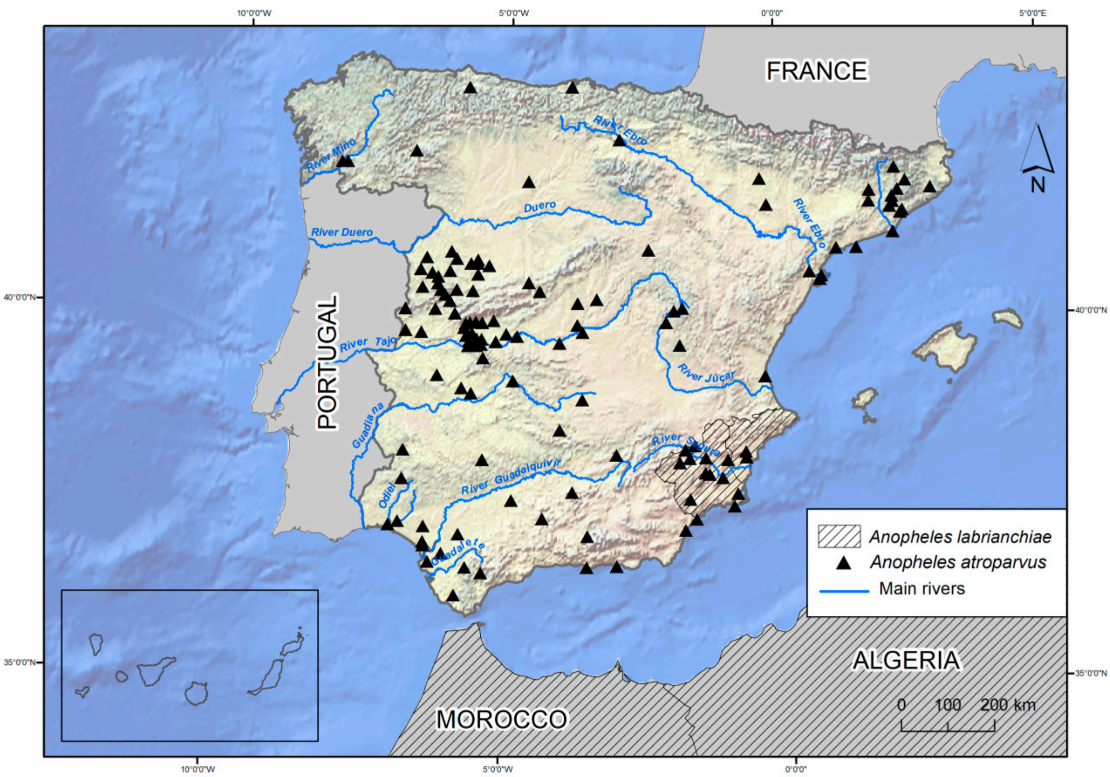

Figure 7. Distribution of localities where the presence of *Anopheles atroparvus* and *Anopheles labranchiae* was recorded, represented by black triangles and cross-hatched areas, respectively (elaborated from [39,41–43]).

The epidemic outbreak that took place during the Spanish post-war period led to a re-launching of sanitary campaigns for control of the mosquito in 1943 [42]. *Anopheles labranchiae* was associated with the rice fields of southeastern Spain; in 1946, it was still abundant in a restricted area of Alicante and Murcia, and it disappeared in 1973 due to the abandonment of rice cultivation, the use of pesticides and the improved draining of the wetlands and other water bodies [40,42,63,64]. Although *Anopheles labranchiae* is an abundant species throughout the African coast between Ceuta and Tangier (including Morocco), it has not been able to settle back in the rice fields and wetlands of the eastern coast of Spain, as it did in the past [65]. This aspect is still relevant, since *Anopheles labranchiae* is present in the neighbouring countries of North Africa. Traditionally, the Mediterranean coastal regions of Spain (such as the Balearic Islands, Valencia, Murcia and even Eastern Andalusia) had a migratory flow of Spanish workers to and from Algeria. In fact, between 1882 and 1914, there was an estimated average seasonal flow of 19,000 travellers and farmers who returned to Spain at the end of the agricultural season [31]. In the early 20th century, the migratory movement from southeastern Spain to Algeria favoured the propagation of malaria. Later, these population flows were among the factors that potentiated the epidemic of the Spanish Civil War [15]. Moreover, the distribution of vectors in the transition between Europe and North Africa could also be related to the post-war epidemic, since many troops from the north of Morocco travelled to Spain through the southwest of the Iberian Peninsula. Therefore, the existence of important population flows and the proximity of the African coast are additional factors that must be considered when analysing the risk of re-emergence of introduced malaria in Spain [11].

3.3.4. Antimalarial Dispensaries during the Epidemic Outbreak of 1937–1947

During the Spanish Civil War (1936–1939) and the later epidemic episode, there were cases of people killed by malaria at the national scale (Figure 1), although there are no complete records of morbidity at the regional or provincial scale. Therefore, we used the data from the antimalarial dispensaries as a source of information for the period 1932–1945. Figure 8a shows the evolution of the number of antimalarial dispensaries and the number of infected people they recorded in the whole of Spain for the period 1932–1945. On the other hand, Figure 8b presents the evolution of the number of infected people recorded by the antimalarial dispensaries in the Spanish regions with higher morbidity levels for that period.

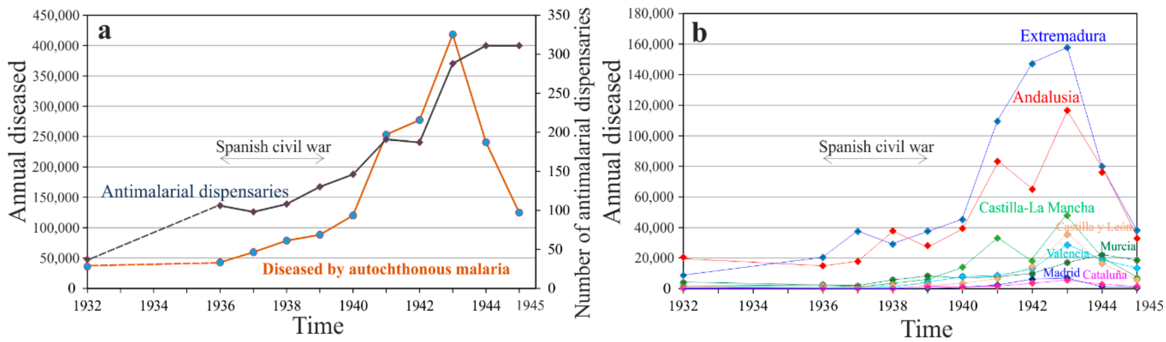

Figure 8. (**a**) Evolution of all antimalarial dispensaries and number of infected people they recorded in Spain from 1932 to 1945. (**b**) Evolution of number of infected people recorded by antimalarial dispensaries from 1932 to 1945 in different regions.

Figure 8a shows that the number of antimalarial dispensaries increased with the number of infected people they recorded. This increase was more pronounced after the Spanish Civil War (1936–1939), when the construction of sanitary infrastructure began. During the war, there were only small increases of morbidity in Extremadura in 1937 and in Western Andalusia in 1938 (Figure 8b). These two regions had the highest concentration of infected people in the whole country for the entire period of 1932–1945. The epidemic outbreak in the post-war period (approximately 1939–1944) appears clearly reflected in almost all regions, especially in Extremadura and all over Andalusia (Figure 8b).

Furthermore, in all Spanish regions, the largest number of infected people occurred in 1943, whereas the largest number of deaths occurred in 1942 (see Figure 1a). In any case, the lethality of the disease increased from 3 per thousand in 1936 to 6 per thousand in 1942 [15]. In the specific case of Andalusia and Castile-La Mancha, there was an outstanding punctual decrease in the number of cases in 1942. An epidemic peak of malaria was also reported in the neighbouring country of Portugal, unlike other European countries in approximately that period [12].

This temporal analysis is completed with a spatial analysis, at the provincial scale, of the number of infected people recorded by the antimalarial dispensaries. In this respect, Figure 9 shows the provincial data of 1932 (before the Spanish Civil War), 1937 (during the conflict with the war fronts stabilised), 1941 (at the beginning of the epidemic peak) and 1945 (when the epidemic outbreak was regressing).

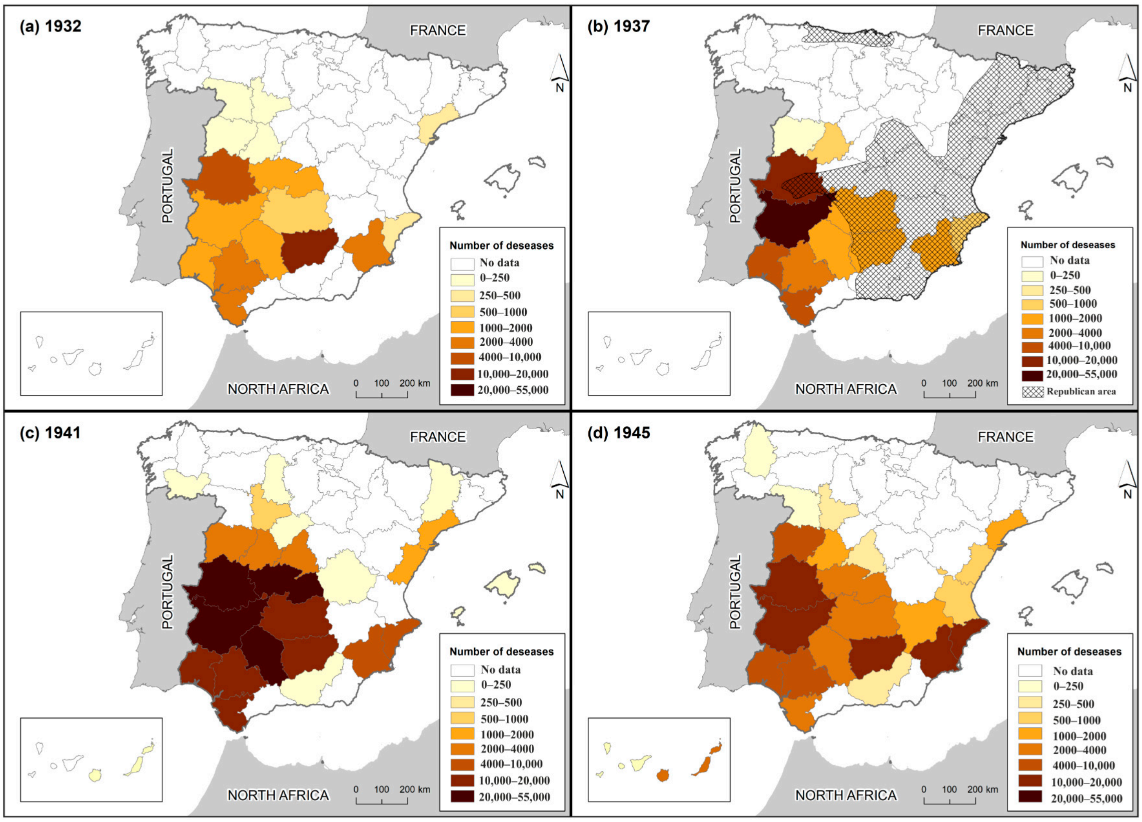

Figure 9. Spatial distribution of number of infected people assisted in each Spanish province in antimalarial dispensaries in the period 1932–1945: (**a**) 1932; (**b**) 1937; (**c**) 1941; and (**d**) 1945. The year 1937 includes the approximate location of the war fronts occupied by the republican side (cross-hatched area) and the national side (without cross-hatch) in March 1937.

The situation in 1932 (Figure 9a) represents the nuclei where most of the cases in Spain were concentrated (Extremadura, Western Andalusia and Murcia-Alicante). From 1936, and especially in 1937, the movement of troops and the destruction of cities created new outbreaks of malaria in areas where there were anophelines, which at that time did not have the protozoan [47]. In fact, the health indicators began to report the worsening of conditions from autumn 1937, and from August 1938, due to problems with the food supply and transportation derived from the conflict [47]. The movement of troops from North Africa to the centre of Spain may have influenced this moderate re-emergence of the disease in traditionally endemic areas, such as Western Andalusia and Extremadura (Figures 8b and 9b). In any case, the epidemiological link with the troops that joined the war from North Africa (a former Spanish colony) is an aspect that should be analysed in more detail in future studies. In this sense, the cases of malaria recorded in Morocco reached a maximum of over 350,000 infected people in 1939, remaining a large number until 1947, when 303,000 cases of infection and 548 deaths were recorded [66].

After the Spanish Civil War (Figure 9c), the disease spread to Northern and Eastern Spain (possibly favoured by population movement and the movements of troops of the two armies involved in the conflict). After the peak phase of this epidemic outbreak (1942–1943), the number of cases began to decrease (Figure 9d). Again, this process was slower in the traditionally more endemic regions and provinces, such as Extremadura, Murcia-Alicante and Western Andalusia. In some provinces, such as Córdoba and Cádiz, the presence of war prisoners and work battalions related to the war period (1936–1945) [44] may have contributed to greater morbidity (Figure 9c).

In addition to the food deficit and the deterioration or disorganisation of hygienic–sanitary infrastructure, other factors that may have influenced this epidemic outbreak are the arrival of infected people in regions that were free of malaria and the incorporation of both parasite carriers and healthy populations from other regions into malarial areas [15]. Thus, the war period had a destructive effect on the sanitary antimalarial system, which worsened the epidemic intensity associated with large population displacement, hunger, the massive arrival of Moroccan troops, the scarcity of medicines and the alteration of the environment [16]. Many of these problems persisted, years later, during the post-war period.

4. Conclusions

This study contributes to the knowledge about the spatiotemporal distribution of malaria in Spain, which was not homogeneous in the 20th and 21st centuries. In the 20th century, most of the cases of autochthonous malaria were concentrated in the regions of Extremadura, Western Andalusia and Murcia-Levante [45]. In fact, between 1916 and 1930, 77% of the people who died of autochthonous malaria were localised in only 20% of the Spanish provinces. Moreover, in 1932, 88% of the infected people assisted by antimalarial dispensaries were concentrated in these regions (especially in the provinces of Cáceres and Murcia). This heterogeneous distribution was influenced by different environmental factors, the socioeconomic and hygienic–sanitary conditions of some regions, the presence of unhealthy water bodies and the distribution of the two historically relevant species of anophelines associated with the transmission of malaria in Spain [3,26,40,45,51].

Throughout time, autochthonous malaria in Spain has shown episodes of epidemic re-emergence, especially in the periods 1917–1922 and 1939–1944, both influenced by war conflicts, population movement and worsening hygienic–sanitary conditions. Although meteorological variables did not play a key role in these epidemic episodes, they did contribute by creating suitable conditions for their intensification. However, the results of this study are limited by the lack of continuity, in the historical archives, of sick people and deaths data available at provincial and infra-provincial level. Despite that, this study shows the great potential of data from antimalarial dispensaries to reconstruct the historical epidemiology of malaria in Spain, and in other countries, especially when there are no available data from other sources corresponding to small towns or counties.

Shortly after the eradication of autochthonous malaria in Spain in 1961, cases of imported malaria began to be reported from 1973, up to over 700 annual cases in the 2010s. Since the anopheline vectors were still present, especially *Anopheles atroparvus*, the cases of imported malaria could cause secondary transmission in Spain, although the possibility of re-emergence of endemic transmission is very low [23], as long as the socioeconomic and hygienic–sanitary conditions of the country do not deteriorate. In this study, it is worth highlighting that the harsh economic conditions that led to budget cuts to the healthcare systems of some European countries in 2008 were accompanied by the re-emergence of climate-sensitive infectious diseases, including malaria [67,68], for example, in Greece [69,70].

The risk of climate change worsening the prevalence of autochthonous malaria in areas where it is limited by low temperatures is a topic that is under current debate [35,51,71], since the influence of temperature on the development of malaria seems to be non-linear, and thus increased temperature variations, when the maximum approaches the higher limit of the vector and the pathogen, will tend to reduce transmission [68]. On the other hand, increased daily temperature variations near the minimum limit can increase transmission, and therefore the morbidity of the disease [68], as was the case in Spain in the mid-20th century with the intra-annual variation of morbidity [51]. Therefore, although epidemic outbreaks of some infectious diseases are influenced by the local climate, it is much more complex to establish how these could be affected by climate change in the long term [71].

The appearance of cases of imported malaria in temperate countries where it had been eradicated [69], such as France, Italy, Greece and Spain, emphasise the interest in improving our knowledge of the epidemiology of the disease in the 20th and 21st centuries. Furthermore, although the risk of transmission of malaria could be affected by climatic factors, there are other factors that play key roles in the evolution of the disease. Among such factors, we can highlight the functioning of healthcare systems, changes in the use of soils and regulations related to urbanisation and construction, which allow for very a low probability of malaria re-emergence in most European countries [72,73].

The history of the disease shows the importance of maintaining vigilance [3,26] and increasing research, especially in swampy areas [17,74], where there are populations of potential anopheline vectors. Changes in the distribution of vectors and in their capacity to transmit pathogens due to climate change will be more evident in zones located in the limit of their distribution area [3]. This could be the case of southeastern Spain, due to its proximity to northern Morocco and Algeria, where the presence of *Anopheles labranchiae* is still being reported. Modern research must delve into the historical conditions of the disease and its historical distribution [75]. Therefore, studies that analyse the spatial distribution of malaria with the aid of GIS tools can help to identify the main factors that have potentiated its eradication in the past and provide valuable information to endemic malaria countries.

Author Contributions: Conceptualisation, A.S. and L.G.-B.; methodology for historical data on indigenous and imported malaria, A.S. and J.M.; mathematical and statistical analysis methodologies, L.G.-B. and A.S.; methodology, GIS and climatic data, M.A.-A. and M.V.; revisualisation, M.V. and M.A.-A.; investigation and resources, A.S., J.M., M.A.-A. and M.V.; writing—original draft preparation, and A.S., L.G.-B. and J.M.; writing—review and editing, A.S., J.M. and M.A.-A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

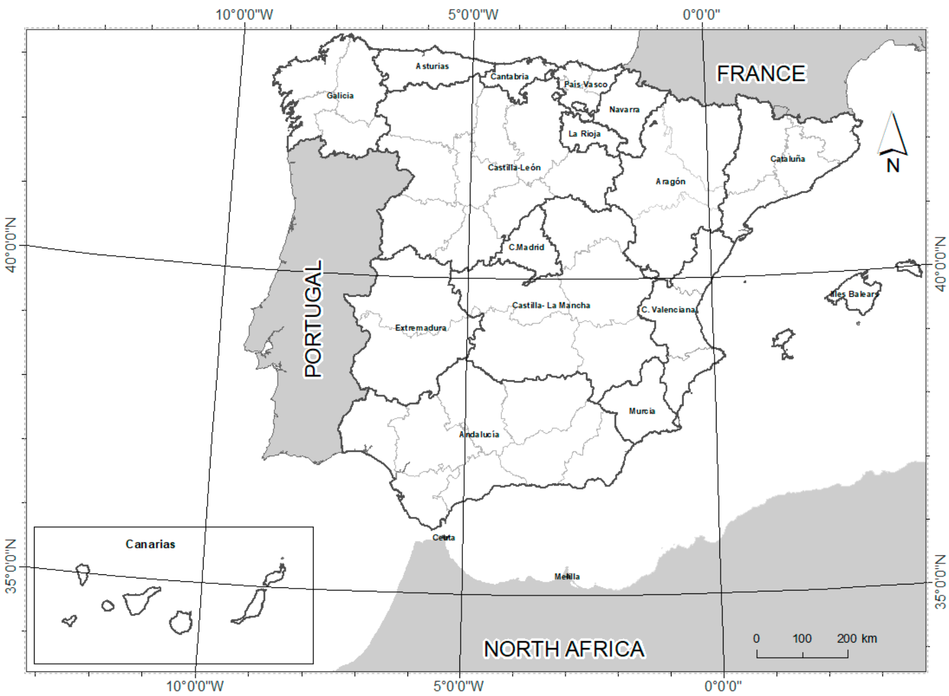

Figure A1. Map of the current regions of Spain.

Figure A2. Map of the provinces of Spain.

References

1. López-Vélez, R.; Molina Moreno, R. Cambio climático en España y riesgo de enfermedades infecciosas y parasitarias transmitidas por artrópodos y roedores. *Rev. Esp. Salud Púb.* **2005**, *79*, 177–190. [CrossRef]
2. Medlock, J.M.; Leach, S.A. Effect of climate change on vector-borne disease risk in the UK. *Lancet Infect. Dis.* **2015**, *15*, 721–730. [CrossRef]
3. Iriso Calle, A.; Bueno-Marí, R.; De las Heras, E.; Lucientes, J.; Molina, R. Cambio climático en España y su influencia en las enfermedades de transmisión vectorial. *Rev. Salud Ambient.* **2017**, *17*, 70–86.
4. Sutherst, R.W. Global Change and Human Vulnerability to Vector-Borne Diseases. *Clin. Microbiol. Rev.* **2004**, *17*, 136–173. [CrossRef] [PubMed]
5. Sutherst, R.W. Implications of global change and climate variability for vector-borne diseases: Generic approaches to impact assessments. *Proc. Int. J. Parasitol.* **1998**, *28*, 935–945. [CrossRef]
6. Bueno-Marí, R.; Jiménez-Peydró, R. Global change and human vulnerability to vector-borne diseases. *Front. Physiol.* **2013**, *6*. [CrossRef]
7. McGregor, G.; Ebi, K. El Niño Southern Oscillation (ENSO) and Health: An Overview for Climate and Health Researchers. *Atmosphere* **2018**, *9*, 282. [CrossRef]
8. WHO. *World Malaria Report 2017*; World Health Organization: Geneve, Switzerland, 2017.
9. Petersen, E.; Severini, C.; Picot, S. Plasmodium vivax malaria: A re-emerging threat for temperate climate zones? *Travel Med. Infect. Dis.* **2013**, *11*, 51–59. [CrossRef]
10. Díaz, J.; Ballester, F.; López-Vélez, R. Impacts on Human Health. In *A Preliminary General Assessment of the Impacts in Spain Due to the Effects of Climate Change*; Moreno Rodríguez, J.M., Ed.; Ministerio de Medio Ambiente: Madrid, Spain, 2005; pp. 699–741.
11. Sousa, A.; García-Barrón, L.; Vetter, M.; Morales, J. The historical distribution of main malaria foci in Spain as related to water bodies. *Int. J. Environ. Res. Publ. Health* **2014**, *11*, 7896–7917. [CrossRef]
12. Zhao, X.; Smith, D.L.; Tatem, A.J. Exploring the spatiotemporal drivers of malaria elimination in Europe. *Malar. J.* **2016**, *15*, 122. [CrossRef]
13. Rubio-Cirilo, L.; Martín-Ríos, M.D.; De Las Casas-Cámara, G.; Andrés-Prado, M.J.; Rodríguez-Caravaca, G. Enfermedades de declaración obligatoria: Conocimiento y notificación en el ámbito hospitalario. *Enferm. Infecc. Microbiol. Clin.* **2013**, *31*, 643–648. [CrossRef]
14. Instituto Español de Estadística Informes anuales del Instituto Español de Estadística (SSIbase). Available online: https://www.ine.es/inebaseweb/libros.do?tntp=25687 (accessed on 17 January 2020).

15. Rico-Avelló, C. La epidemia de paludismo de la postguerra. *Rev. Sanid. Hig. Públ.* **1950**, *24*, 701–737.
16. Rodriíguez Ocanña, E.; Añón, B.; Perdiguero Gil, E.; Medina Doménech, R.M.; Molero Mesa, J. *La Accion Medico-Social Contra El Paludismo En La Espana Metropolitana Y Colonial Del Siglo XX*; Consejo Superior de Investigaciones Cientiíficas: Madrid, Spain, 2003; ISBN1 84-00-08184-6. ISBN2 978-84-00-08184-3.
17. Sousa, A.; Andrade, F.; Félix, A.; Jurado, V.; León-Botubol, A.; García-Murillo, P.; García-Barrón, L.; Morales, J. La importancia histórica de los humedales del suroeste de España en la transmisión de la malaria. *Limnetica* **2009**, *28*, 283–300.
18. Sousa, A.; García-Barrón, L.; García-Murillo, P.; Vetter, M.; Morales, J. The use of changes in small coastal Atlantic brooks in southwestern Europe as indicators of anthropogenic and climatic impacts over the last 400 years. *J. Paleolimnol.* **2015**, *53*, 73–88. [CrossRef]
19. Navarro, M.; Navaza, B.; Guionnet, A.; López-Vélez, R. Chagas Disease in Spain: Need for Further Public Health Measures. *PLoS Negl. Trop. Dis.* **2012**, *6*, e1962. [CrossRef] [PubMed]
20. Chowell, G.; Erkoreka, A.; Viboud, C.; Echeverri-Dávila, B. Spatial-temporal excess mortality patterns of the 1918-1919 influenza pandemic in Spain. *BMC Infect. Dis.* **2014**, *14*, 371. [CrossRef] [PubMed]
21. Bulletins del Instituto Carlos III y la española Red Nacional de Vigilancia Epidemiología . Available online: http://revista.isciii.es/index.php/bes (accessed on 20 January 2020).
22. Sistema Básico de Vigilancia Comunitat Valenciana. Available online: http://www.sp.san.gva.es/DgspPortal/docs/epidemiologia/casos_tasas_anuales.htm (accessed on 20 January 2020).
23. Herrador, Z.; Fernández-Martínez, B.; Quesada-Cubo, V.; Díaz-García, O.; Cano, R.; Benito, A.; Gómez-Barroso, D. Imported cases of malaria in Spain: Observational study using nationally reported statistics and surveillance data, 2002–2015. *Malar. J.* **2019**, *18*, 230. [CrossRef]
24. Rotaeche Montalvo, V.; Hernández Pezzi, G.; de Mateo Ontañón, S. Vigilancia epidemiológica del paludismo en España, 1996–1999. *Semer. Med. Fam.* **2001**, *27*, 438–442. [CrossRef]
25. Nicolau, R. Población, Salud y Actividad. In *Estadísticas Históricas de España: Siglos XIX-XX*; Carreras, A., Tanunell, X., Eds.; Fundación BBVA: Bilbao, Spain, 2005; Volume I, pp. 77–154.
26. Bueno-Marí, R.; Jiménez Peydró, R. Malaria en España: Aspectos entomológicos y perspectivas de futuro. *Rev. Esp. Salud Publ.* **2008**, *82*, 467–479. [CrossRef]
27. García-Barrón, L.; Camarillo, J.M.; Morales, J.; Sousa, A. Temporal analysis (1940-2010) of rainfall aggressiveness in the Iberian Peninsula basins. *J. Hydrol.* **2015**, *525*, 747–759. [CrossRef]
28. García-Barrón, L.; Morales, J.; Sousa, A. A new methodology for estimating rainfall aggressiveness risk based on daily rainfall records for multi-decennial periods. *Sci. Total Environ.* **2017**, *615*, 564–571. [CrossRef] [PubMed]
29. García-Barrón, L.; Aguilar-Alba, M.; Morales, J.; Sousa, A. Intra-annual rainfall variability in the Spanish hydrographic basins. *Int. J. Climatol.* **2018**, *38*, 2215–2229. [CrossRef]
30. García-Barrón, L.; Aguilar-Alba, M.; Sousa, A. Evolution of annual rainfall irregularity in the southwest of the Iberian Peninsula. *Theor. Appl. Climatol.* **2011**, *103*, 13–26. [CrossRef]
31. Carreras, A.; Tafunell, X. *Estadísticas Históricas de España, Siglos XIX-XX. Volumen I.*; Fundación BBVA: Bilbao, Spain, 2005; ISBN 84-96515-01-X.
32. Schiewe, J. Empirical studies on the visual perception of spatial patterns in choropleth maps. *KN J. Cartogr. Geogr. Inf.* **2019**, *69*, 217–228. [CrossRef]
33. Omumbo, J.A.; Hay, S.I.; Goetz, S.J.; Snow, R.W.; Rogers, D.J. Updating historical maps of malaria transmission intensity in East Africa using remote sensing. *Photogramm. Eng. Remote Sens.* **2002**, *68*, 161–166.
34. Sipe, N.G.; Dale, P. Challenges in using geographic information systems (GIS) to understand and control malaria in Indonesia. *Malar. J.* **2003**, *2*, 1–8. [CrossRef]
35. Hay, S.I.; Cox, J.; Rogers, D.J.; Randolph, S.E.; Stern, D.I.; Dennis Shanks, G.; Myers, M.F.; Snow, R.W. Regional warming and malaria resurgence: Commentary. *Nature* **2002**, *420*, 628. [CrossRef]
36. Guerra, C.A.; Snow, R.W.; Hay, S.I. Mapping the global extent of malaria in 2005. *Trends Parasitol.* **2006**, *22*, 353–358. [CrossRef]
37. Bui, H.T.N.; Niederwieser, I.; Bird, M.J.; Dai, W.; Brancucci, N.M.B.; Moes, S.; Jenoe, P.; Lucet, I.S.; Doerig, C.; Voss, T.S. Mapping and functional analysis of heterochromatin protein 1 phosphorylation in the malaria parasite Plasmodium falciparum. *Sci. Rep.* **2019**, *9*, 1–15. [CrossRef]

38. Gwitira, I.; Murwira, A.; Masocha, M.; Zengeya, F.M.; Shekede, M.D.; Chirenda, J.; Tinago, W.; Mberikunashe, J.; Masendu, R. GIS-based stratification of malaria risk zones for Zimbabwe. *Geocarto Int.* **2019**, *34*, 1163–1176. [CrossRef]
39. Eritja, R.; Aranda, C.; Padrós, J.; Goula, M.; Lucientes, J.; Escosa, R.; Marquès, E.; Cáceres, F. An annotated checklist and bibliography of the mosquitoes of Spain (Diptera: *Culicidae*). *Eur. Mosq. Bull.* **2000**, *8*, 10–18.
40. Delacour, S.; Melero-Alcibar, R.; Aranda, C.; Cortés, M.; Eritja, R.; Escosa, R. Detailed maps of the geographical distribution of the mosquitoes of Spain based on a literature review. Part II: Genus Anopheles. In Proceedings of the the 5th European Mosquito Control Association Workshop, Turín, Italy, 9–13 March 2009.
41. Santa-Olalla Peralta, P.; Vázquez-Torres, M.C.; Latorre-Fandós, E.; Mairal-Claver, P.; Cortina-Solano, P.; Puy-Azón, A.; Adiego Sancho, B.; Leitmeyer, K.; Lucientes-Curdi, J.; Sierra-Moros, M.J. First autochthonous malaria case due to Plasmodium vivax since eradication, Spain, October 2010. *Eurosurveillance* **2010**, *15*, 19684. [CrossRef] [PubMed]
42. Bueno-Marí, R.; Bernués-Bañeres, A.; Jiménez-Peydró, R. Updated checklist and distribution maps of mosquitoes (Diptera: Culicidae) of Spain. *J. Eur. Mosq. Control Assoc.* **2012**, *30*, 91–126.
43. Barrado, L.; Ezpeleta, C.; Rubio, J.M.; Martín, C.; Azcona, J.M.; Arteaga, M.; Beristain, X.; Navascués, A.; Ongay, E.; Castilla, J. Source identification of autochthonous-introduced Plasmodium vivax Malaria, Spain. *Infection* **2017**, *45*, 111–114. [CrossRef] [PubMed]
44. García-Funes, J.C. *Espacios De Castigo Y Trabajo Forzado Del Sistema Concentracionario Franquista*; Universidad Pública de Navarra: Pamplona, Spain, 2017.
45. Sousa, A.; García-Barrón, L.; Aguilar-Alba, M.; Vetter, M.; Morales, J. The importance of wetlands and unhealthy water bodies in the distribution of malaria in Spain. In *Advances in Sustainable and Environmental Hydrology, Hydrogeology, Hidrochesmestry and Water Reosurces*; Chaminé, H.I., Barbieri, M., Kisi, O., Chen, M., Merkel, B.J., Eds.; Springer: Cham, Switzerland, 2019; ISBN 978-3-030-0157-8.
46. Trilla, A.; Trilla, G.; Daer, C. The 1918 "Spanish Flu" in Spain. *Clin. Infect. Dis.* **2008**, *47*, 668–673. [CrossRef] [PubMed]
47. Barona, J.L.; Perdiguero-Gil, E. Health and the war. Changing schemes and health conditions during the Spanish civil war. *Dynamis* **2008**, *28*, 103–126. [CrossRef] [PubMed]
48. Teklehaimanot, H.D.; Lipsitch, M.; Teklehaimanot, A.; Schwartz, J. Weather-based prediction of Plasmodium falciparum malaria in epidemic-prone regions of Ethiopia I. Patterns of lagged weather effects reflect biological mechanisms. *Malar. J.* **2004**, *3*, 41. [CrossRef]
49. Bi, Y.; Yu, W.; Hu, W.; Lin, H.; Guo, Y.; Zhou, X.N.; Tong, S. Impact of climate variability on Plasmodium vivax and Plasmodium falciparum malaria in Yunnan Province, China. *Parasites Vectors* **2013**, *6*, 357. [CrossRef]
50. Piperaki, E.T.; Daikos, G.L. Malaria in Europe: Emerging threat or minor nuisance? *Clin. Microbiol. Infect.* **2016**, *22*, 487–493. [CrossRef]
51. Sousa, A.; Morales, J.; Vetter, M.; Aguilar-Alba, M.; García-Barrón, L. Influence of monthly temperatures on the intra-annual distribution of autochthonous malaria in Spain. *Recent Advances in Environmental Science from the Euro-Mediterranean and Surrounding Regions*, 2020; Springer: Cham, Switzerland, 2020; in press.
52. WHO. *World Malaria Report 2011*; World Health Organization: Geneva, Switzerland, 2011.
53. Millet, J.P.; De Olalla, P.G.; Gascón, J.; Prat, J.G.I.; Treviño, B.; Pinazo, M.J.; Cabezos, J.; Muñoz, J.; Zarzuela, F.; Caylà, J.A. Imported malaria among African immigrants: Is there still a relationship between developed countries and their ex-colonies? *Malar. J.* **2009**, *8*, 111. [CrossRef]
54. García-Villarrubia, M.; Millet, J.P.; De Olalla, P.G.; Gascán, J.; Fumadá, V.; Gómez, I.; Prat, J.; Treviño, B.; Pinazo, M.J.; Cabezos, J.; et al. Epidemiology of imported malaria among children and young adults in Barcelona (1990–2008). *Malar. J.* **2011**, *10*, 347. [CrossRef] [PubMed]
55. Antinori, S.; Napolitano, M.; Grande, R.; Passerini, S.; Ridolfo, A.L.; Galimberti, L.; Oreni, L.; Schinaia, S.; Milazzo, L.; Galli, M.; et al. Epidemiological and clinical characteristics of imported malaria in adults in Milan, Italy, 2010–2015. *Eur. J. Intern. Med.* **2018**, *57*, e13–e16. [CrossRef] [PubMed]
56. Tatem, A.J.; Jia, P.; Ordanovich, D.; Falkner, M.; Huang, Z.; Howes, R.; Hay, S.I.; Gething, P.W.; Smith, D.L. The geography of imported malaria to non-endemic countries: A meta-analysis of nationally reported statistics. *Lancet Infect. Dis.* **2017**, *17*, 98–107. [CrossRef]
57. Norman, F.F.; López-Polín, A.; Salvador, F.; Treviño, B.; Calabuig, E.; Torrús, D.; Soriano-Arandes, A.; Ruíz-Giardín, J.M.; Monge-Maillo, B.; Pérez-Molina, J.A.; et al. Imported malaria in Spain (2009–2016): Results from the +REDIVI Collaborative Network. *Malar. J.* **2017**, *16*, 407. [CrossRef] [PubMed]

58. Domínguez García, M.; Feja Solana, C.; Vergara Ugarriza, A.; Bartolomé Moreno, C.; Melús Palazón, E.; Magallón Botaya, R. Imported malaria cases: The connection with the European ex-colonies. *Malar. J.* **2019**, *18*, 397. [CrossRef]
59. Khuu, D.; Eberhard, M.L.; Bristow, B.N.; Javanbakht, M.; Ash, L.R.; Shafir, S.C.; Sorvillo, F.J. Economic impact of malaria-related hospitalizations in the United States, 2000–2014. *J. Infect. Publ. Health* **2019**, *12*, 424–433. [CrossRef]
60. Moyo, Q.M.; Besser, M.; Lynn, R.; Lever, A.M.L. Persistence of Imported Malaria into the United Kingdom: An Epidemiological Review of Risk Factors and At-risk Groups. *Clin. Infect. Dis.* **2018**, *69*, 1156–1162. [CrossRef]
61. Kendjo, E.; Houzé, S.; Mouri, O.; Taieb, A.; Gay, F.; Jauréguiberry, S.; Tantaoui, I.; Ndour, P.A.; Buffet, P.; Piarroux, M.; et al. Epidemiologic trends in malaria incidence among travelers returning to metropolitan France, 1996–2016. *JAMA Netw. Open* **2019**, *2*, e191691. [CrossRef]
62. Fernández López, M.; Ruiz Giardín, J.M.; San Martín López, J.V.; Jaquetti, J.; García Arata, I.; Jiménez Navarro, C.; Cabello Clotet, N. Imported malaria including HIV and pregnant woman risk groups: Overview of the case of a Spanish city 2004–2014. *Malar. J.* **2015**, *14*, 356. [CrossRef]
63. Blazquez, J.; De Zulueta, J. The disappearance of Anopheles labranchiae from Spain. *Parassitologia* **1980**, *22*, 161–163.
64. Ramsdale, C.; Snow, K. Distribution of the genus Anopheles in Europe. *Eur. Mosq. Bull.* **2000**, *7*, 1–26.
65. Bueno-Marí, R.; Jiménez-Peydró, R. New anopheline records from the Valencian Autonomous Region of Eastern Spain (Diptera: *Culicidae: Anophelinae*). *J. Eur. Mosq. Control Assoc.* **2010**, *28*, 148–156.
66. WHO. *World Malaria Report 2010*; World Health Organization: Geneva, Switzerland, 2010.
67. Karanikolos, M.; Mladovsky, P.; Cylus, J.; Thomson, S.; Basu, S.; Stuckler, D.; MacKenbach, J.P.; McKee, M. Financial crisis, austerity, and health in Europe. *Lancet* **2013**, *381*, 1323–1331. [CrossRef]
68. Smith, K.R.; Woodward, A.; Campbell-Lendrum, D.; Chadee, D.D.; Honda, Y.; Liu, Q.; Olwoch, J.M.; Revich, B.; Sauerborn, R.; Confalonieri, U.; et al. Human health: Impacts, adaptation, and co-benefits. In *Climate Change 2014 Impacts, Adaptation and Vulnerability: Part A: Global and Sectoral Aspects*; Cambridge University Press: Cambridge, UK, 2015; pp. 709–754. ISBN 9781107415379.
69. Danis, K.; Lenglet, A.; Tseroni, M.; Baka, A.; Tsiodras, S.; Bonovas, S. Malaria in Greece: Historical and current reflections on a re-emerging vector borne disease. *Travel Med. Infect. Dis.* **2013**, *11*, 8–14. [CrossRef]
70. Andriopoulos, P.; Economopoulou, A.; Spanakos, G.; Assimakopoulos, G. 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.* **2013**, *17*, e125–e128. [CrossRef] [PubMed]
71. Patz Hulme, M.; Rosenzweig, C.; Mitchell, T.D.; Goldberg, R.A.; Githeko, A.K.; Le Sueur, D.J.A. Climate change (Communication arising): Regional warming and malaria resurgence. *Nature* **2002**, *420*, 627–628. [CrossRef]
72. Semenza, J.C.; Menne, B. Climate change and infectious diseases in Europe. *Lancet Infect. Dis.* **2009**, *9*, 365–375. [CrossRef]
73. Wolf, T.; Lyne, K.; Martínez, G.; Kendrovski, V. The health effects of climate change in the WHO European Region. *Climate* **2015**, *3*, 901–936. [CrossRef]
74. Kuhn, K.G.; Campbell-Lendrum, D.H.; Armstrong, B.; Davies, C.R. Malaria in Britain: Past, present, and future. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 9997–10001. [CrossRef]
75. Huldén, L.; Huldén, L.; Heliövaara, K. Endemic malaria: An “indoor” disease in northern Europe. Historical data analysed. *Malar. J.* **2005**, *4*, 19. [CrossRef]