

The Spatiotemporal Distribution of Historical Malaria Cases in Sweden: A Climatic Perspective

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Case study

Keywords: malaria, epidemic, history, infectious disease, GIS, summer temperature, summer precipitation, Sweden

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RESEARCH

The spatiotemporal distribution of historical malaria cases in Sweden: a climatic perspective

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Abstract

Background: Understanding of the impacts of climatic variability and change on human health, and the spread of diseases, remains poor despite an increasing burden of vector-borne diseases under global warming. Many confounding social variables make such studies challenging during the modern period while studies of climate–disease relationships in historical times are constrained by a lack of long-term data sets. Previous studies of malaria in historical times have revealed an association with climate in northern Europe. Yet, malaria in Sweden in relation to climate variables is understudied and relationships have never been rigorously statistically established. This study seeks to examine the relationship between malaria and climate fluctuations using several data sources, and to characterise the spatio-temporal variations at parish level during severe malaria years in Sweden between 1749 and 1859.

Methods: Pearson (r_p) and Spearman's rank (r_s) correlation analyses were conducted to evaluate inter-annual relationship between malaria deaths, temperature and precipitation. The climate response to larger malaria events was further explored by Superposed Epoch Analysis, and through Geographic Information Systems analysis to map spatial variations of malaria deaths.

Results: The number of malaria deaths showed the most significant positive relationship with warm-season temperature of the preceding year, but less significant against precipitation. The strongest correlation was found between malaria deaths and the mean temperature of the preceding June–August ($r_s=0.57$, $p<0.01$) during the 1756–1820 period. Most malaria hot-spots, during severe malaria years, concentrated in areas around big inland lakes and southern-most Sweden.

Conclusions: Increases in malaria transmission, and hence malaria deaths, in Sweden was linked to high summer temperature during the preceding year. This relationship can be established with statistical confidence from parish records in tandem with the long meteorological series. Our results indicate that unusually warm and/or dry summers may have contributed to malaria epidemics, but with non-linear characteristics, highlighting the difficulties in modeling climate–malaria associations. The inter-annual spatial variation of malaria hot-spots further shows that malaria outbreaks were more pronounced in the southern-most region of Sweden in the first half of the nineteenth century compared to the second half of the eighteenth century.

Keywords: malaria; epidemic; history; infectious disease; GIS; summer temperature; summer precipitation; Sweden

Introduction

The distribution and abundance of hosts and vectors, and the transmitted pathogens of vector-borne diseases, are strongly influenced by changes in temperature and precipitation [1, 2]. Evidences of outbreaks driven by temperature anomalies in Europe [3], and projected spread of vectors with the presence of warming [4], indicated that the expected increase in global mean temperature, and associated changes in regional climate patterns, will very likely have effects on human health and on the prevalence and distribution of various vector-borne diseases [5].

One of the major human-infecting vector-borne diseases today, malaria, is described to have had tremendous impact on the evolutionary selection of the human genome [6, 7], and it has historically caused the largest amount of human mortality among all infectious diseases [8]. Malaria is caused by the replication of parasites of the genus *Plasmodium* in the human blood and transmitted between humans by mosquitoes of the genus *Anopheles*. Malaria was widespread across Europe, including the Scandinavian countries, until the mid to late nineteenth century, and was in Sweden especially prevalent in coastal areas [9, 10]. Previous studies of malaria in the Scandinavian countries have observed the association between malaria epidemics and climate and weather conditions, in particular summer temperature and hydrological extremes [11, 12, 9]. The combination of anomalously high rainfall, followed by warm summers and drought, likely created favourable habitats for the *Anopheles* larvae and hence increased malaria transmission. Characteristic seasonal cycles in the fluctuation of malaria cases during severe malaria years were also identified with significant peaks occurring in late spring (April–May) and early autumn (September–October) [11]. Furthermore, except for these weather-related events at inter-annual time-scales, decades with warm summers appear to coincide with peaks of malaria incidence across northern Europe [13, 14]. Among the Scandinavian countries, the disease has been best studied in Finland, where a strong relationship between malaria outbreaks and preceding summer temperature was established for the nineteenth century [15]. It was concluded that summer temperature was determinant for mosquito population, consequently reflecting transmission frequency. Yet, from a long-term perspective, malaria is capable of transmitting indoors throughout the year despite the presence of cold weather and strong climatic fluctuations. Notably, long-term warming at higher latitudes did not have any decisive influence on malaria dynamics in the long run [15, 13] as has been predicted by some malaria models [16, 17].

The decline of malaria in Europe has been entirely attributed to factors other than climate. Yet to track the change in climate suitability in areas of potential risk for malaria transmission is of global importance [18]. The uncertainties regarding vector-borne diseases affected by climatic drivers highlight the need for local datasets covering long periods of time, to develop better empirical models [19], and allow to quantify the assessment of the sensitivity of the disease in relation to both climatic and non-climatic factors [20]. However, except for Finland, data in the other Scandinavia countries is sparse and the status of the malaria history of Sweden is obsolete. Moreover, to capture the heterogeneity at regional scale which

often poses a great location-specific sensitivity to climate has been a challenge in modeling climate–disease relationship [21, 22]. In light of a possible geographical shift in malaria incidence due to the ongoing anthropogenic climate change, gaining better knowledge of past climate–malaria relationship is of great relevance and may even have policy implications for disease surveillance at national level.

Thus, the aim of this study is to examine the effects of short-term climate fluctuations on malaria based on historical data from Sweden, and with the application of GIS tools to trace the spatiotemporal variations of malaria hot-spot, which can provide useful information to investigations of controlling socioeconomic factors. In this study, we statistically establish the link between the main climate variables (temperature and precipitation) and the inter-annual to decadal dynamics of malaria, and reveal the regional variation of more severe malaria epidemics at a fine spatial resolution during the eighteenth and nineteenth centuries.

State-of-the-art

Change and variability of climate affects human health and the spread of diseases, in various ways, on intra-annual to multi-decadal and even centennial time-scales [23]. Extreme weather events affect the health for, in particular, the poorer and more vulnerable segments of the population [24]. Changes in temperature and precipitation, as well as in the frequency and duration of extreme climate and weather events directly affect human health, e.g. by increased mortality during heatwaves [25], and even comparably small changes in temperature and/or precipitation can result in measurable impacts on diseases [26]. However, most climate-related health risks are associated to secondary climatic influences, such as shifting patterns of disease vectors or food production, water supplies, social disruption, and migration [27, 28, 29]. Therefore, studies of human health vulnerability in relation to changing climate need to include both direct and indirect impacts of climate change [30].

Today malaria is almost exclusively found in tropical regions, with an estimated present-day prevalence of more than 200 million cases per year [31]. However, up until the early twentieth century, malaria also plagued people in temperate climates, and it was endemic up to the Arctic Circle in Scandinavian and European Russia. Historically malaria was introduced to Europe and established throughout the continent [32], with the increase in trade and shipping it spread soon to new regions [9]. Since then, malaria remained endemic in Sweden, with evidence pointing to the existence of a former Scandinavian strain of the malaria parasite, *Plasmodium vivax* [33]. This *P. vivax* strain phenotype was described to have a prolonged incubation time of 8–10 months until primary infection, and long latency phases of up to 9 years until relapse were commonly reported [34, 35]. This scandinavian *P. vivax* strain, which is extinct today, was presumably closely related to the *P. vivax hibernans* strain, isolated in Russia in 1949 [34, 36]. In 1982 the dormant hypnozoite stage of *P. vivax*, permitting the relapse of malaria, was first identified [37]. However, molecular cues inducing relapse of *P. vivax* from hypnozoites to the symptomatic erythrocytic stage remain largely unknown. Several hypotheses have been proposed to explain *P. vivax*'s survival during hibernation and the transmission of

the parasite after winter in regions with highly seasonal climate such as northern Europe.

Importantly, recent findings suggests that *Plasmodium* parasites are able to adjust infection and relapse behavior to the presence of endemic mosquitoes which is indirectly dictated by climatic conditions [34, 35, 38]. A study on historical malaria in Finland proposed that *P. vivax* potentially detects the presence of *Anopheles* vectors and thereby adjusts transmission timing. This would allow the parasite to stay in the dormant hypnozoite state until vector season, circumventing transmission limitations by unstable climatic conditions [34]. However, empirical experiments to evaluate the validity of this hypothesis remains to be performed. Additionally, the survival and spread of the *Plasmodium* parasite were possibly facilitated by co-habitation of infected, hibernating mosquitoes in strongly climate-controlled environments together with humans during the winter season [15]. Thus, the mosquito vector plays a crucial role to the understanding of historical seasonality, infection and relapse of *P. vivax* malaria in northern Europe.

In Sweden, the genus *Anopheles* is represented by eight species [39, 40]. The species that historically have been involved in malaria transmission belong to the *An. maculipennis* complex, which consists of closely related species that are difficult to identify based on morphological characters [41]. This includes the species *Anopheles (Anopheles) messeae* Falleroni 1926, which was considered to have been the main vector of malaria in Sweden as well as other countries with similar climatic conditions such as Finland, parts of Russia and other regions of the former Soviet Union [34, 39, 41, 42]. It also includes *Anopheles (Anopheles) atroparvus* van Thiel 1927, which is the proposed vector of malaria in the coastal regions of southern Sweden due to its preference to brackish larval habitat [41].

During spring and summer, *An. messeae* and *An. atroparvus* females prefer to rest and blood-feed indoors on large domestic animals, e.g. livestock, but will occasionally also feed on humans [43]. The larvae can be found in a number of stagnant water bodies, such as flood-plains, edges of rivers and lakes, ditches, and ponds. Both of these *Anopheles* species spend the winter season as inseminated females e.g. in stables or abandoned buildings. *An. messeae* remain inactive throughout winter while *An. atroparvus* may irregularly take blood-meals without laying eggs [43]. It has been proposed that *Plasmodium* sporozoites can alter the behaviour of infected mosquitoes, leading to increased blood-feeding behavior which would optimize transmission during the winter months [42].

Clearly, the relationship between vectors and climate conditions is significant but highly complex. Climate change-related components, especially the warming trend and certain extreme weather events such as heat-waves, are believed to increase the burden of vector-borne diseases [44, 45]. Temperature and precipitation are the two primarily, and most widely studied, climate indicators in relation to malaria. Ambient temperature is crucial for sporogony development as well as a key driver in mosquito population dynamics. A temperature increase of a few degrees Celsius

can result in an expanded geographical range of *P. vivax* beyond their usual limits in the north, and in a larger population size of infectious *Anopheles* mosquitoes [46]. Precipitation variations, correspondingly, alter the aquatic habitats for mosquitoes and predators, but the evidence of malaria outbreaks associated with precipitation is quite mixed and context-specific [47]. As the climate–disease relationship is often shaped in complicated mechanisms, multiple climate variables related to temperature and hydroclimate need to be taken into account from a biological perspective [16, 48].

Malaria in Sweden has been eradicated, and the country was officially declared malaria-free in 1963 [49], following the last reported endemic malaria case in 1939 [50]. Today malaria only occurs as imported cases in Sweden [51], a situation similar to elsewhere in Europe [52, 53, 54, 55]. The decrease in malaria transmission has been attributed to factors such as the use of quinine, improved living conditions, the change to outdoor livestock sheds, improved drainage, and more efficient healthcare [56]. In addition, it has been speculated that the comparably low summer temperatures during the eighteenth and nineteenth centuries perhaps also played a role in the long-term decline in malaria transmission [12, 46]. However, this explanation appears highly questionable since palaeoclimate records show colder conditions during the seventeenth century [57, 58, 29].

Methods

Data assembly

Obtaining historical primary source material that addresses diseases or mortality in a particular disease is challenging, especially records covering more distant time periods. To study the long-term variations of a disease, data from different sources are commonly combined to overcome the limits set by the short data coverage and/or an uneven geographical distribution of the source material. In this study, cases of malaria-attributed deaths in Sweden are mainly derived from data obtained from digitised parish records. Datasets available in older publications were also digitised. Following exploratory data analysis, the following three data sources were selected for this study:

- 1) The Tabellverket (1749–1859) dataset: Under the name Tabellverket, vital statistics, including the cause of death, were collected in Sweden from 1749 to 1859 and registered at parish level. As government officials, the priests of the Lutheran Church of Sweden were responsible for filling out the forms for their parish [59]. Several different forms were given out between 1749 and 1859, and the causes of death were specified in a list, containing between 33 and 41 categories, depending on the form used at the time. Regarding malaria, the Swedish term *frossa*, with various spellings, or the more symptomatic descriptive term *remittent fevers* was used to describe malaria. However, for the 1831–1859 period the causes of death had to be written down in the priests own wording for most diseases [60]. From 1860 onwards, routines changed and physicians were to write death certificate for all deaths in cities, while priests still reported the causes of death in the countryside. Reports on deaths from certain common diseases were then communicated to the newly formed

government agency Statistics Sweden (*Statistiska centralbyrån*). Reported deaths by these diseases were then summarised at county level in official yearly publications, and one of the diseases listed in the publications was malaria [61]. Analysing causes of death in historic times in Sweden back to 1749 were facilitated by the digitalisation of all surviving Tabellverket forms by the Demographic Database (DDB) at Umeå University. However, comparisons between the DDB digitised data from Tabellverket and the statistical summaries from the time the original data was collected show that the digitised data from Tabellverket under-register death rates, most likely because all forms of vital statistics have not survived throughout the years [62]. In spite of the shortcomings, the digitised data from Tabellverket can still be considered a great asset for assessing the cause of death at parish level from 1749 to 1859 and to track the changes over time in the frequency of death in common diseases. In total, 90,178 cases of malaria deaths (i.e. symptoms typically described in Swedish as *frossa*, *fråssa*, *omväxlande feber*, *frosse* and *remittent febrar*) were extracted from the Tabellverket database over the 1749–1859 period.

2) The Bergman (1749–1820) dataset: A table of mortality attributed to malaria in Sweden was published by the Swedish physician, Gustaf Bergman [11]. This table combined data from Tabellverket, with some periods commonly shared by Sweden and present-day Finland prior to 1809 (when Finland still was still part of Sweden). The Bergman [11] data was digitised for the purpose of comparison with the Tabellverket data, digitised by the Demographic Database (DDB) at Umeå University, and to supplement it.

3) The Flensburg (1826–1890) dataset: A total number of 10,443 malaria cases were collected by Dr. Carl Flensburg from the military hospital in Stockholm [12]. These cases are malaria patients who had been treated in the hospital. It did thus not include patients not treated in the hospital. The data were digitised from Flensburg's original article [12].

The *frossa* diagnosis

As mentioned above, for a long time, *frossa* was the common name for malaria in Sweden. For example, the Swedish cause of death nomenclature from 1911 states that *Frossa* (*Febris intermittens*) should be written in official statistics, while the associated list for doctors stated the Latin equivalent *malaria* for the same disease [63]. The Swedish disease name *frossa* then existed alongside its Latin translation in official nomenclature up until the implementation of ICD-9 (International Classification of Diseases) in 1987 [64]. Before that, however, it had since long been replaced with malaria as an everyday expression for this disease. Prior to the discovery of the *Plasmodium* parasite in 1880, diagnosing was conducted through symptom observations. In general, *frossa* was divided into three different types, referring to how often the fever chills recurred, denoted as *quotidiana* (daily), *tertian* (every second day), *quartana* (every third day). The main symptoms associated with the diagnosis was chills and hot flushes [65]. However, the provincial physicians linked the *frossa* diagnosis with a wide spectrum of symptoms. Apart from irregular fever flushes, the most frequently observed symptoms were headaches, nausea, joint pains and

diarrhea. Less frequently, it was associated with respiratory symptoms, and one physician associated dropsy and abdominal infarctions with malaria [66]. Moreover, the use of quinine to treat malaria seem to have been fairly widespread in the mid-nineteenth century [67]. However, already in early-eighteenth century writings on malaria, the quinine treatment was mentioned in Swedish publications [65]. It was noticed that sickness in malaria was higher in areas with marshland and swamps. As modern medical theories did not emerge until late nineteenth century, physicians adopted their observations into the theory of miasma, taking on that pathogenic vapours emerging from the wetlands caused the disease [68].

Historical meteorological data

Monthly temperature data from Stockholm (1756–1890) [69] and Uppsala (1722–1890) [70] were used for comparison with the three malaria datasets. The Stockholm and Uppsala stations are approximately 70 km apart from each other, and they show similar summer temperature fluctuations ($r_p = 0.93$ during 1826–1890 for June–July). Temperature data from both places were homogenised, but an additional adjustment was applied to the Stockholm data to eliminate the warm bias of the thermometer’s exposure to solar radiation [71]. Monthly precipitation data from Stockholm (1756–1890) and Uppsala (1722–1890) were obtained from the Swedish Meteorological and Hydrological Institute (SMHI) [72].

The malaria time-series and the meteorological data were all standardised over their respective periods to show anomalies. The standardised value was calculated using the following formula:

$$\text{Standardised value} = \frac{X - \mu}{\sigma}$$

where:

X = the value of an observation

μ = the mean

σ = the standard deviation

Georeferencing the data

After the data of malaria-attributed deaths were collected from the digitised data from Tabellverket, they were sorted and summarised by each parish and year using Feature Manipulation Engine (FME) version 2020 by Safe Software [73]. The conversion of malaria records to spatially resolved data was achieved by matching the existing parish name with the historical parish georeferenced data from the Swedish National Archives (Riksarkivet). The closest matches were first automatically identified using the function *levenshtein* in the open source Geographic Information Systems (GIS) software QGIS [74], and a few identified mismatches were corrected through an additional manual inspections by the authors.

Mapping of annual malaria-attributed deaths

Annual malaria-attributed deaths from each parish in the digitised georeferenced data from Tabellverket were used to produce heat maps to demonstrate the spatial-temporal variations in the number of malaria-attributed deaths. This was performed

using the built-in heat-map function in QGIS [74]. By defining a circular neighborhood around the center of each data point, the program will find the number of the points within this neighborhood, creating a density raster of these data points by interpolation (kernel density estimation) according to the colour ramp user customized. For our data, each data point was given the same weight regardless of the number of deaths reported from the same parish, which allows to emphasise the variations in spatial pattern instead of the strength of respective outbreaks. A radius of 25 kilometers was specified for visualizing a more generalized density pattern from year to year. The higher number of data points found in a particular area can be viewed as an area with higher malaria-attributed death density.

Correlation analysis

Both Pearson (r_p) and Spearman rank (r_s) correlation analysis were performed to analyze the correlation between the number of malaria-attributed deaths and monthly and seasonal temperature and precipitation data. Pearson correlation is better suited to evaluate linear relationships between two variables, while Spearman rank correlation analysis is performed based on the ranked values for each variable, with a better ability to measure non-linear responses between variables. We envisioned that the Spearman rank correlation might be better suited especially in cases of extremely high numbers of malaria-attributed death during severe epidemics.

Superposed epoch analysis

Superposed Epoch Analysis (SEA) [75] was employed to test whether anomalous climate conditions had a significant impact in years with particularly high numbers of malaria-attributed deaths. Standardised temperature anomalies, calculated by dividing the standard deviation (SD) for all event years, were compared to the five years prior to and the following years with most recorded malaria deaths/cases. We performed the SEA using a custom developed program written in F77-Fortran, and estimated the 0.05 significance level through 1000 randomisations, and also made several tests of the malaria key selection for the outcome. We present the Gaussian mean values from the SEA, having found in an exploratory data analysis that the results were similar to using the median and the bi-weight robust means.

Results

The spatial distribution of the 90,178 cases of malaria-attributed deaths in Sweden between 1749–1859, retrieved from the digitised Tabellverket dataset compiled at parish level is presented in Fig. 1. The map shows that malaria-attributed deaths, and thus presumably transmission hot-spots, were located mainly on the eastern, but also western coastal areas, around large inland lakes, and in the southern-most part of Sweden. Combined with the data of Bergman and Flensburg, more than one hundred years of variations in malaria cases/deaths in Sweden during 1749–1859 are presented in Fig. 2. The most severe nationwide epidemic period occurred 1827–30, with malaria-attributed deaths reaching almost 20,000 cases. Other notable time periods with elevated malaria cases/deaths include 1758, 1776–1777, 1810, 1812 and 1821–1822. Severe malaria outbreaks in the capital city of Stockholm can be seen in the Flensburg data in 1827–1828, 1831, 1840, 1847–1848 and 1854–1857.

Climatic drivers

The climatic parameter and season associated with increased frequency of malaria were identified by means of Pearson and Spearman's rank correlation analyses (Table 1). Positive correlations were found with the May–August temperature of the preceding year. The highest correlation was observed with July temperature of the preceding year, while the monthly combination with the strongest correlation between malaria and temperature was June–July. Correlation with August temperature was less strong, but still significant in the Flensburg dataset. This relationship is much weaker in the data from Tabellverket due to a sharp decrease in available data after 1831. Nevertheless, the calculation using the common period with Bergman's dataset, which is limited to 1820, gives comparable results. Among different malaria datasets, the strongest correlation was found between Bergman's series of malaria-attributed deaths and the mean temperature of July–August during the preceding year ($r_s=0.57$, $p<0.01$) over the period of 1756–1820. Precipitation, in contrast to temperature, generally showed negative correlations with the number of malaria-attributed deaths. The most significant correlations were found for June–July precipitation during the preceding year ($r_p/r_s=-0.26/-0.45$, $p<0.05/0.01$). The correlations with May–July (MJJ) and June–August (JJA) precipitation were also strong but only found using Spearman's rank correlation, implying a more non-linear relationship.

Effect of anomalously warm temperatures

The occurrence of severe malaria events in response to climate anomalies over the entire 1749–1859 period was further tested by Superposed Epoch Analysis (SEA) assessing the years with most recorded malaria-attributed deaths. The results indicate that the peak years of malaria-attributed deaths were significantly (confidence interval=95%) associated with positive anomalies in temperature of May–July and June–August of the preceding year (Fig. 3). The impact of negative anomalies in precipitation of the preceding year on years with many malaria-attributed deaths also appears in some, but not all, of the datasets (not shown).

Spatial variations of severe malaria epidemics

We evaluated the spatial distribution, at parish level, of malaria-attributed deaths from Tabellverket during 1749–1859, the 20 years with the highest recorded deaths within the borders of present-day Sweden. The relative geographic distribution of malaria-attributed deaths is shown in heat maps with focus on the southern part of Sweden where most deaths were recorded. During these 20 years (Fig. 4), hot-spots were recognised around Lake Mälaren, Lake Vänern, and in big cities and their surroundings. To a certain extent the density of deaths is reflecting population density at the time. However, the region just north of Lake Mälaren and the plains of Östergötland, in the east, as well as Skåne in southern-most Sweden, show disproportionately high numbers of malaria-attributed deaths relative to these regions' share of the population.

Each of those 20 years with the most recorded malaria-attributed deaths, representing the major malaria outbreak years in Sweden 1749–1859, reveal somewhat

different geographical patterns of malaria mortality. The four major years with most malaria-attributed deaths in the eighteenth century – 1757, 1758, 1776, and 1777 – showed a concentration of malaria mortality around Lake Mälaren and in Östergötland, with only a modest mortality in densely populated Skåne. A similar pattern is evident for the early-nineteenth century years 1811, 1812, and 1820. Conversely the major centre of malaria-attributed deaths in 1830 and 1832 was in Skåne (Fig. 4).

During some years the malaria mortality was geographically confined to certain portions of Sweden, with little evidence of malaria mortality in other parts of the country. This was particularly the case 1757–1758, 1776–1777, and 1820. During other years, most notably 1822–1826, malaria-attributed deaths were geographically widespread across southern and central Sweden. In conclusion, the heat-map analysis reveals distinct patterns of malaria-attributed deaths, and thus presumably also the relative occurrence of malaria cases, shifting over time independent of the relative population density that remained comparable stable over the study period.

Discussion

Comparison of different datasets

In Bergman's study, he used data over malaria-attributed deaths from Tabellverket, which should have yielded the same result as the digitised Tabellverket data employed in this study. However, before 1801 malaria-attributed death reported by Bergman's death numbers are twice the number reported in Tabellverket's data, while peak years with elevated malaria death were slightly lower in Bergman's data. This discrepancy might be explained by the loss of records, and that our studies have attributed slightly different causes as malaria deaths. Nevertheless, there is a very high correlation between the digitised data from Tabellverket and the data by Bergman ($r_p=0.88$ for the common period 1749–1820), and the fluctuations are rather comparable between these two datasets. However, given the differences, we consider it appropriate to present both datasets on malaria deaths in our analysis.

Missing data

In the official data from Tabellverket used in our analysis, for every year there is a lack of data from certain parishes. An estimated 20% of death records are missing in the digitised data by Tabellverket when comparing to the contemporary official documentation at a national level [76]. For data of malaria-attributed deaths, a substantial part of the original data after 1830 is unfortunately missing. This can be attributed to the fact, that only smallpox and neonatal death were specified on the form used during 1831–1859; other causes of deaths, including malaria, was not specified on the pre-printed forms. The priests therefore needed to report the cause of death manually. Hence, the data during the 1831–1859 period is incomplete. However, the decrease in malaria transmission by the end of the 19th century is evident from the data by Flensburg of malaria cases treated at the Stockholm military hospital. Since the number of military personnel was always 2,700 men, his data is considered to show a reliable trend over time. Flensburg later complemented the data to include all malaria cases, including noted cases from the military barracks

not treated in the hospital, but the continuity of this data varies between years. In this data (not shown), 2,632 men were infected with malaria in 1828, which was consistent with the 1827–30 peak of malaria-related mortality in the data from Tabellverket. It is worth to again stress that the records on causes of death after 1831 were not complete, and Flensburg hence had to collect the data from *Sundhetskollegii årsberättelse* and from the publications of the Swedish Association of Medicine (*Svenska läkaresällskapets handlingar*) to compile the malaria cases in the entire country of Sweden between 1861 and 1909. His table show 11,074 malaria cases were recorded in 1861, the most severe malaria year during this period. Other malaria years were 1862, 1873–1874, and 1877 during this period.

The temperature and precipitation data from Stockholm and Uppsala used in this study are among the longest meteorological observations in the world [77], but the precipitation data is neither continuous nor as reliable as the temperature data. In particular, the precipitation data from Stockholm 1859–1862, 1864–1870, 1880–1890, and from Uppsala 1863–1868 and 1878–1890 contain some questionable values. Monthly data from Uppsala is also occasionally missing in 1764–1773. Besides the concern about data continuity, the Stockholm temperature data displays considerably lower summer temperature values than Uppsala in the period prior to 1859, likely due to the warm bias adjustment in the process of homogenisation. This could be one explanation to why Flensburg's malaria data from Stockholm shows higher correlation with temperature data from Uppsala compared to Stockholm (as would be expected).

Malaria dynamics and summer temperatures

Malaria epidemics in Sweden usually start with anomalously warm summers and end with cold summers [9], but a recent study showed that non-linearity is often found in malaria dynamics driven by environmental factors, for instance, the strength of the effect of temperature on malaria transmission [78]. This is clearly shown in Fig. 2, that although unusually warm summers are not necessarily connected to severe malaria epidemics, the start of several major epidemic outbreaks coincided with anomalously warm summers during the preceding 1–2 years. These epidemic years were 1758, 1776–1777, 1808–1812, 1809–1812, 1820–1830, 1847–1848, and 1854–1856.

Malaria dynamics and hydrological variability

In addition to temperature being an important determinant of its dynamics, malaria is closely linked with the presence of water bodies. To a large extent, the high density of malaria-attributed deaths around large inland lakes and coastal regions of southern Sweden corresponds to the distribution of *Anopheles maculipennis* spp. vectors [9]. The association of malaria spreading with individual weather events is, however, elusive. A connection between malaria years, precipitation and the water level in Lake Mälaren was proposed by Bergman, suggesting that malaria epidemics usually were preceded by one or several years with unusually high rainfall and high lake levels, followed by warm summers often accompanied with droughts. When temporary water bodies form during dry periods, it can create a favorable

aquatic condition for larvae and lead to an increase in mosquito abundance [11]. Although the correlation analyses failed to show a consistent link between malaria and precipitation, the results from the Spearman's rank correlation show stronger correlations between precipitation and malaria compared to Pearson's correlation analysis. This indicates that the influence of precipitation on malaria may not be linear. Furthermore, the dependent relationship of temperature and rainfall (Pearson correlation = -0.4 , 1748–1890, $n = 143$, from Uppsala meteorological station) makes it intractable to clarify the interplay of each factor associated with the number of malaria-attributed deaths. Interestingly, the most severe epidemic period 1820–1830, with a total of 34,659 malaria-attributed deaths in Sweden, coincided with four exceptionally dry years, but not always with warm summers. In short, considering all combined factors, simple correlative methods may not suffice when studying the response of malaria to some climate variables [79], especially if the response is non-linear. Approaches which are able to analyse the causation in a non-linear dynamic system are thus needed in future research to better evaluate the influences of several climate factors simultaneously on malaria.

Comparison with previous studies

The early malaria studies in Sweden, conducted by Bergman (1877) and Flensburg (1911), provide extremely valuable information regarding the association between malaria epidemics and climate dynamics. Their pioneering attempts have helped to clarify the causation based on empirical observations. Bergman used maps to demonstrate the temporal delay of epidemic spread from coastal areas towards inland areas, and towards the north, during certain epidemic periods at a district level. This pattern of the temporal delay is, nevertheless, not distinct during earlier epidemic periods (1749–1831) in our spatial analysis (Fig. 4). Areas of intense transmission in Sweden and Finland were further mapped in Ekblom (1945) [9], in which malaria occurred mainly in the southeast of Sweden, but without such a fine spatial resolution as here. By analysing malaria-attributed deaths at a higher spatial resolution (i.e. parish level), we are for example able to detect that malaria was more prevalent in the southern-most province of Sweden (Skåne) in the nineteenth century compared to the late eighteenth century. During the major outbreak of 1827–1830 in southern Sweden, Denmark similarly saw outbreaks with over 4,235 malaria-attributed deaths [80] in eastern Denmark bordering southern Sweden (Skåne), known for having harbored malaria [81]. Furthermore, records of malaria from the military hospital in Stockholm (the Flensburg dataset) also present peak years estimates comparable with those in southern Finland [15], including the major peak years 1831, 1846–1847 (1847–1848 in Sweden) and 1854–1855 (1854–1857 in Sweden). This shows that severe malaria epidemics were widespread events. In addition, although different malaria datasets have been used, covering different time periods, our results are consistent with earlier studies for Finland [15, 14]. This lends support to the conclusion that the summer temperature during the preceding year had a strong influence on malaria transmission. The use of the Spearman's rank correlation in this study helped to reduce the effect of strong peaks in malaria mortality. This method is also suited to address non-linear relationships, allowing us to carry out an analysis of both the relationships between malaria and temperature

and precipitation. The latter climate variable, showing a more non-linear effect, was not included in the studies for Finland [15, 14].

Conclusions

Increased transmission of malaria in Sweden, and elsewhere in northern Europe, has historically been linked to higher average temperature during the summer of the preceding year. This study of malaria in Sweden during the eighteenth and nineteenth centuries supports such a relationship, i.e., that warm and/or dry summers may have contributed to more severe malaria outbreaks in the following year(s). Likely the warmer than usual temperatures increased the number of malaria vectors, and that symptoms of malaria infection appeared and were documented the following year, due to both indoor winter transmission and the evidenced long incubation and relapse time of the *P. vivax* malaria parasite. The effect of precipitation fluctuations on malaria was, on the other hand, found to be less significant, and likely being non-linear. Malaria hot-spots were concentrated in the areas around Lake Mälaren and the plains of Östergötland in the middle of the eighteenth century, but subsequently became more widespread across southern Sweden, especially in 1822–1826. Moreover, the outbreaks were generally more pronounced in Sweden's southern-most region (Skåne) in the first half of the nineteenth century. These findings improve our knowledge of the history of malaria in Sweden, but also highlight the potential need for modelling malaria's response to climate in a nonlinear dynamical system. The digitised and georeferenced data of malaria-attributed deaths in Sweden, and its distribution at a parish level, allows for further investigations of the dynamics behind malaria outbreaks and the shift of transmission hot-spots with emphasis on possible controlling demographic, social, and economic factors.

Abbreviations

GIS: Geographic Information Systems; FME: Feature Manipulation Engine; SEA: Superposed Epoch Analysis; SD: standard deviation

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Authors' contributions

T.T.C. conceived the study and conducted data analysis. F.C.L. assisted with malaria data compilation, proposed insightful perspectives to the work, carried out SEA analysis and contributed to the writing. H.C., F.H., M.I., J.C.H., J.A., K.S. and H.W.L. contributed to the writing and discussions. H.W.L. supervised the project.

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Availability of data and materials

The data that support the findings of this study are available from Centre for Demographic and Ageing Research (CEDAR) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Centre for Demographic and Ageing Research (CEDAR).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Tables

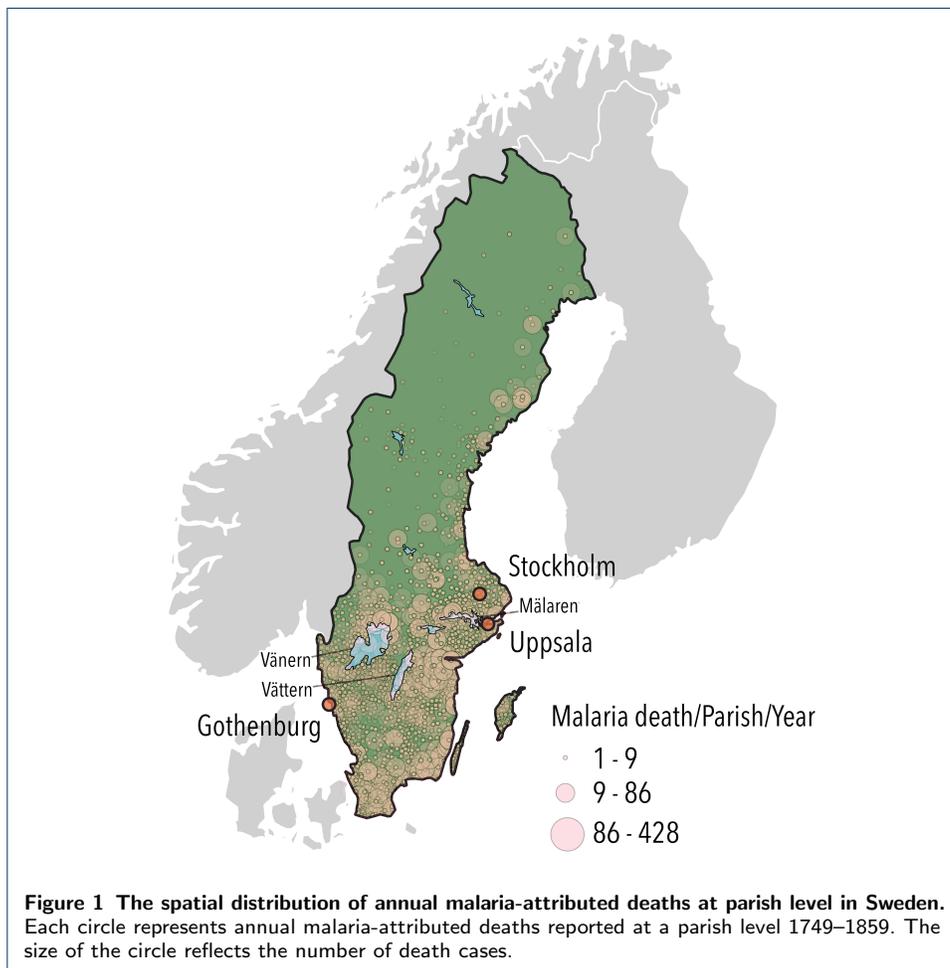


Table 1 Pearson’s correlations/Spearman’s rank correlations (r_p/r_s) between the datasets from Tabellverket (1749–1859), Bergman (1749–1820), Flensburg (1826–1890) and monthly meteorological data of the preceding year from Stockholm (1756–1890) and Uppsala (1748–1890). Bold: $p < 0.05$ significant; *: $p < 0.01$ highly significant

Dataset	Tabellverket		Bergman		Flensburg	
	Stockholm 1756–1859 (104 years)	Uppsala 1749–1859 (111 years)	Stockholm 1756–1820 (65 years)	Uppsala 1749–1820 (72 years)	Stockholm 1826–1890 (65 years)	Uppsala 1826–1890 (65 years)
Temperature						
Apr (-1)	-0.06/0.06	0.00/0.11	-0.04/-0.07	-0.09/-0.09	-0.15/-0.06	-0.02/0.05
May (-1)	0.15/0.12	0.16/0.16	0.20/0.25	0.04/0.14	0.14/0.13	0.18/0.18
Jun (-1)	0.27/0.20	0.24/0.21	*0.48/*0.47	*0.35/*0.35	0.30/0.30	*0.37/*0.40
Jul (-1)	0.15/0.25	0.16*0.31	*0.46/*0.49	*0.42/*0.47	*0.37/0.30	*0.46/*0.40
Aug (-1)	-0.02/0.09	0.01/0.09	0.20/0.28	0.24/0.23	0.27/0.26	*0.32/*0.35
JJ (-1)	0.24/*0.25	0.23/*0.31	*0.53/*0.52	*0.47/*0.47	*0.40/*0.35	*0.50/*0.50
AMJ (-1)	0.15/0.16	0.17/0.22	0.26/0.26	0.10/0.17	0.14/0.12	0.24/0.25
MJJ (-1)	0.24/0.23	0.25/*0.30	*0.48/*0.50	*0.34/*0.39	*0.37/*0.32	*0.46/*0.45
JJA (-1)	0.17/0.21	0.18/0.25	*0.51/*0.57	*0.47/*0.47	*0.42/*0.40	*0.52/*0.54
Precipitation						
Mar (-1)	-0.15/-0.15	-0.09/*-0.27	-0.23/-0.30	-0.07/-0.03	-0.16/-0.26	-0.15/-0.11
Apr (-1)	0.10/0.13	0.09/-0.04	0.20/0.09	*0.33/0.23	-0.11/-0.11	-0.02/0.11
May (-1)	-0.05/0.05	0.08/0.00	-0.06/-0.07	0.29/0.03	-0.07/-0.14	-0.05/-0.06
Jun (-1)	-0.16/-0.11	-0.22/*-0.35	-0.11/-0.20	-0.25/*-0.44	-0.20/-0.24	-0.16/-0.14
Jul (-1)	-0.07/0.00	-0.11/*-0.30	-0.19/-0.29	-0.12/-0.22	-0.20/-0.27	-0.08-0.03
Aug (-1)	0.01/-0.04	-0.03/-0.17	0.14/0.15	0.00/-0.12	0.07/0.03	0.10/0.08
JJ (-1)	-0.15/-0.03	-0.23/*-0.44	-0.20/-0.26	-0.26/*-0.45	-0.28/*-0.37	-0.15/-0.14
MAM (-1)	-0.04/0.05	0.02/-0.12	0.077-0.14	*0.32/0.16	-0.19/-0.24	-0.13/-0.05
AMJ (-1)	-0.09/0.01	-0.05/-0.21	0.05/-0.03	0.14/-0.12	-0.25/-0.27	-0.14/-0.04
MJJ (-1)	-0.13/0.01	-0.15/*-0.34	-0.11/-0.22	-0.10/*-0.34	-0.28/*-0.39	-0.14/-0.16
JJA (-1)	-0.10/-0.01	-0.17/*-0.44	-0.05/-0.03	-0.19/*-0.37	-0.16/-0.25	-0.04/-0.05

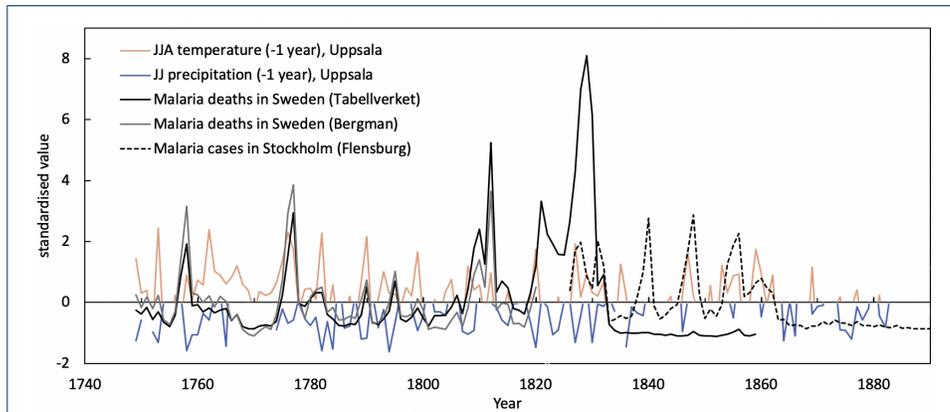


Figure 2 Time-series of malaria datasets against climate variables. Malaria datasets from three data sources (Tabellverket 1749–1859, Bergman 1749–1820, Flensburg Stockholm 1826–1890) and the relations to meteorological data. Malaria-attributed deaths of in the datasets from Tabellverket and Bergman represents the entire country, while Flensburg’s malaria cases were from the capital city, Stockholm. The meteorological data was moved backward with one year (–1). Only positive values of temperature data (orange line) and negative values of precipitation data (blue line) are shown to emphasise the correlations against the malaria datasets. Malaria-attributed deaths in the datasets of Tabellverket and Bergman have been standardised to their common period 1749–1820; the other series are standardised over their own respective period for the purpose of comparison. The drop in the number of malaria-attributed deaths after 1831 in the datasets from Tabellverket is a result of the way death registering had changed, the details are described in the Method section.

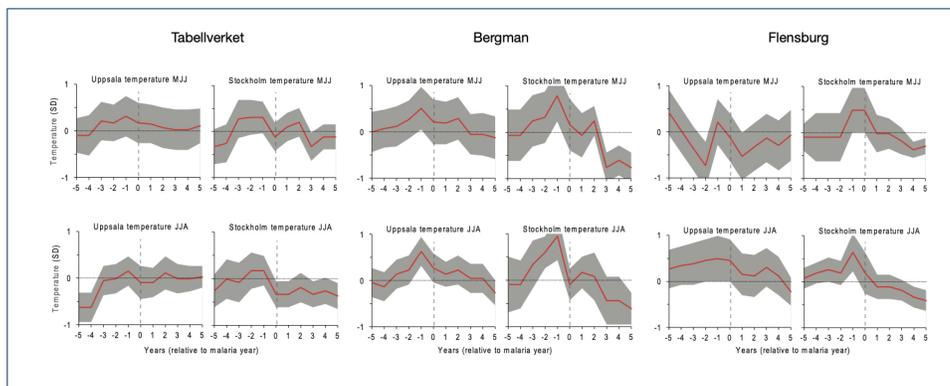
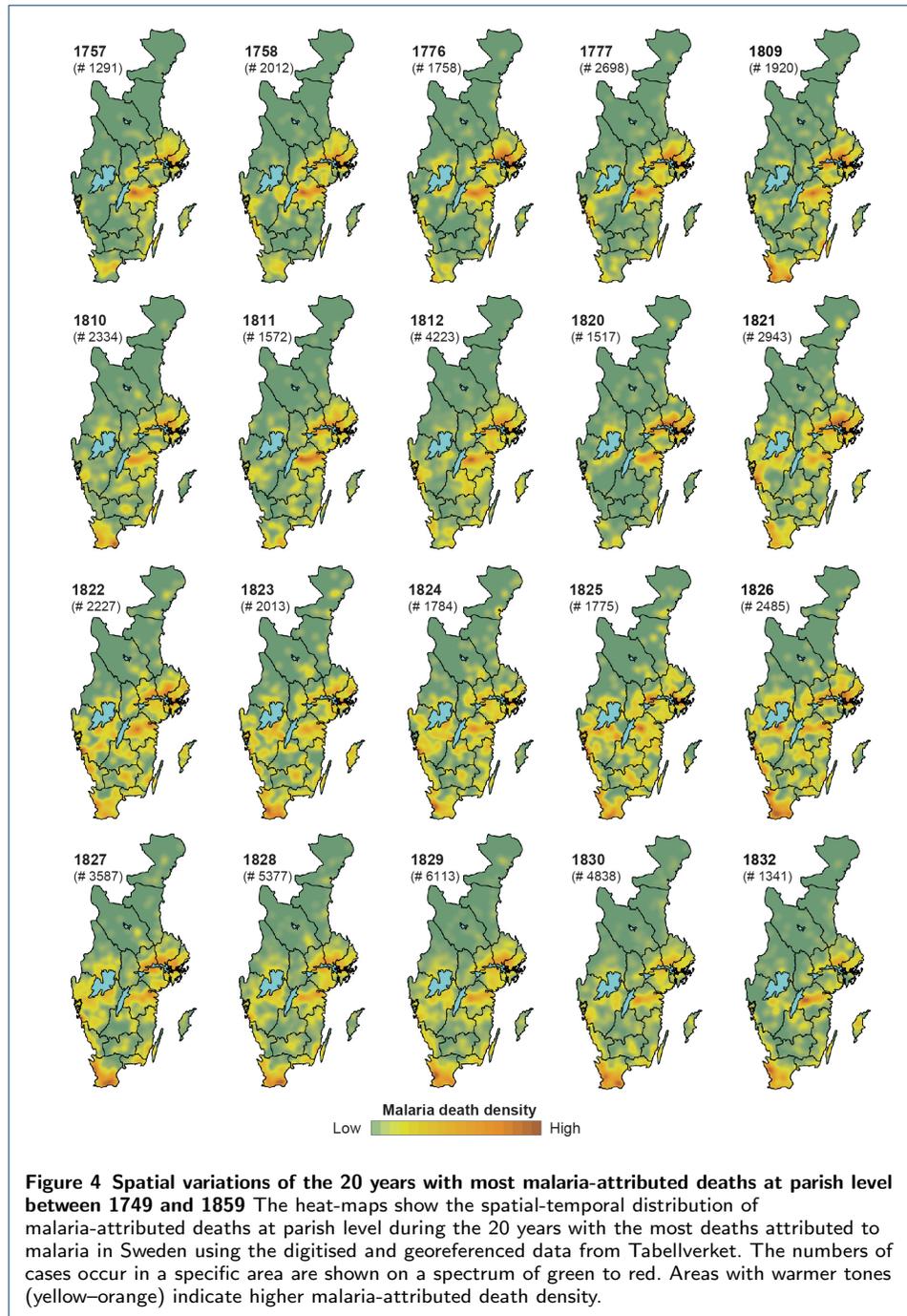


Figure 3 Superposed Epoch Analysis (SEA) Results from the Superposed Epoch Analysis (SEA) for three malaria datasets (Tabellverket, Bergman, and Flensburg), assessing the response of years with the 20 most malaria-attributed deaths (Tabellverket, Bergman) and malaria cases (Flensburg) to warm-season (May–July, June–August) temperature based on all years in the 1749–1859 period. The grey-shaded area represents 95% confidence intervals derived through 1000 randomizations. The results indicate that the peak years of malaria-attributed deaths, or cases, were significantly associated with the preceding warm-season temperature. The magnitude of the climate anomalies are shown as standard deviations (SD).



Figures



Figure 1

The spatial distribution of annual malaria-attributed deaths at parish level in Sweden. Each circle represents annual malaria-attributed deaths reported at a parish level 1749-1859. The size of the circle reflects the number of death cases. Note: The designations employed and the presentation of the

material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

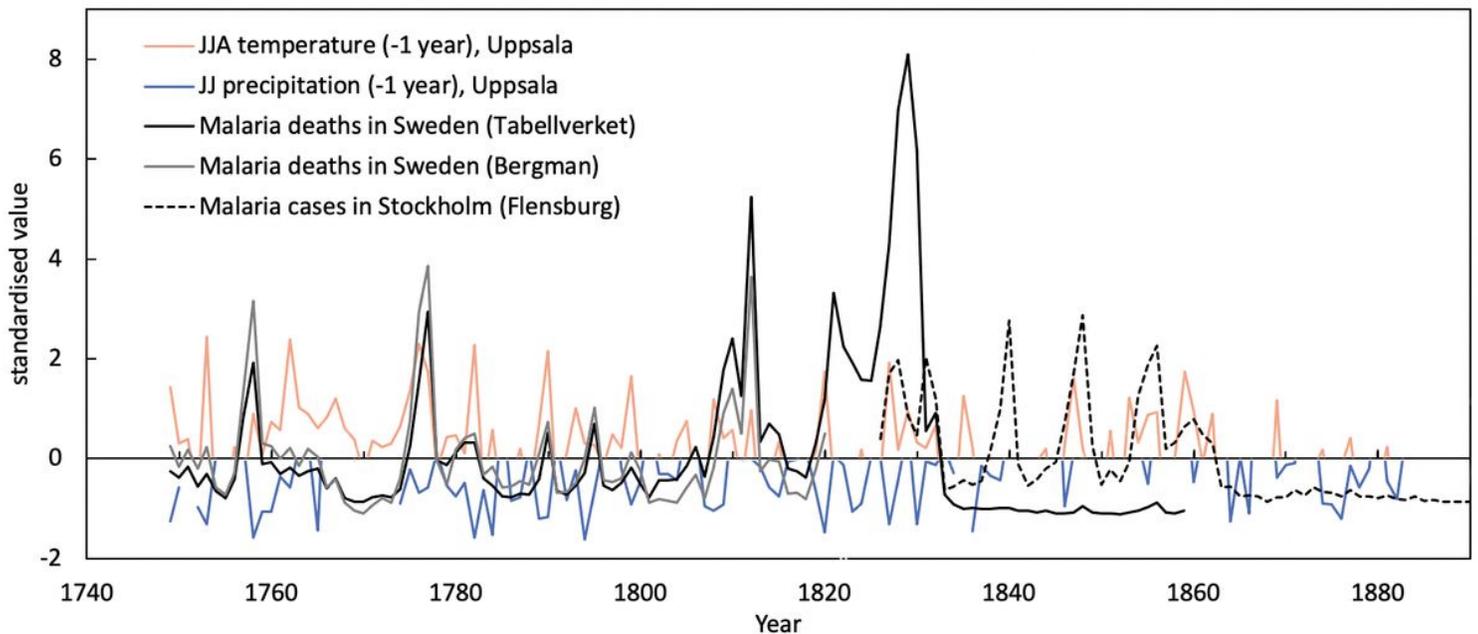


Figure 2

Time-series of malaria datasets against climate variables. Malaria datasets from three data sources (Tabellverket 1749{1859, Bergman 1749-1820, Flensburg Stockholm 1826{1890) and the relations to meteorological data. Malaria-attributed deaths of in the datasets from Tabellverket and Bergman represents the entire country, while Flensburg's malaria cases were from the capital city, Stockholm. The meteorological data was moved backward with one year (-1). Only positive values of temperature data (orange line) and negative values of precipitation data (blue line) are shown to emphasise the correlations against the malaria datasets. Malaria-attributed deaths in the datasets of Tabellverket and Bergman have been standardised to their common period 1749{1820; the other series are standardised over their own respective period for the purpose of comparison. The drop in the number of malaria-attributed deaths after 1831 in the datasets from Tabellverket is a result of the way death registering had changed, the details are described in the Method section.

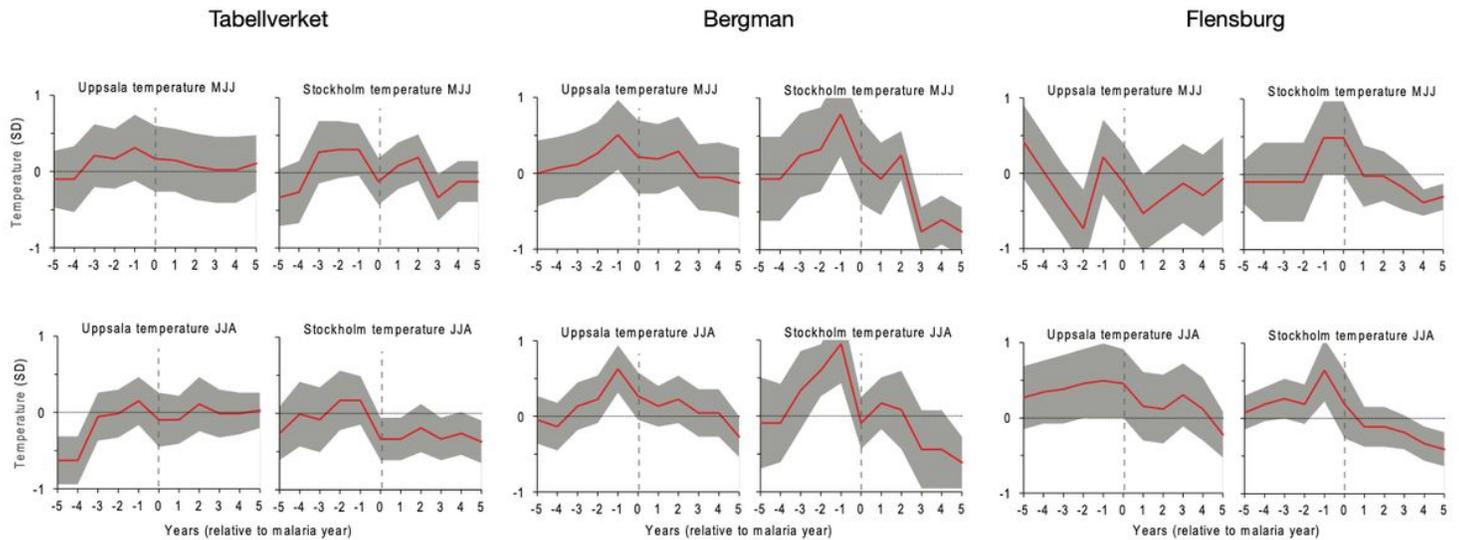


Figure 3

Superposed Epoch Analysis (SEA) Results from the Superposed Epoch Analysis (SEA) for three malaria datasets (Tabellverket, Bergman, and Flensburg), assessing the response of years with the 20 most malaria-attributed deaths (Tabellverket, Bergman) and malaria cases (Flensburg) to warm-season (May-July, June-August) temperature based on all years in the 1749-1859 period. The grey-shaded area represents 95% condence intervals derived through 1000 randomizations. The results indicate that the peak years of malaria-attributed deaths, or cases, were signicantly associated with the preceding warm-season temperature. The magnitude of the climate anomalies are shown as standard deviations (SD). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

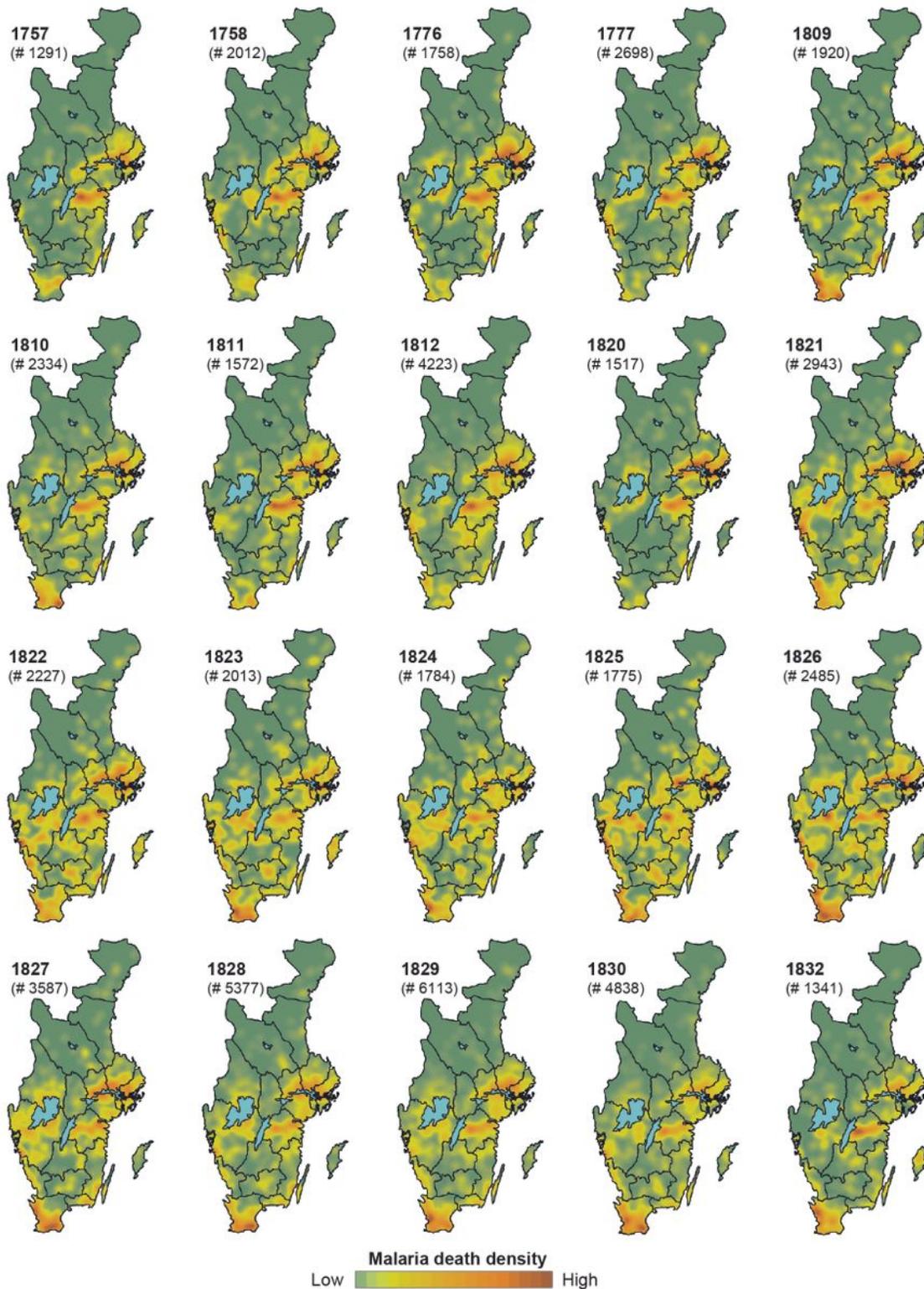


Figure 4

Spatial variations of the 20 years with most malaria-attributed deaths at parish level between 1749 and 1859. The heat-maps show the spatial-temporal distribution of malaria-attributed deaths at parish level during the 20 years with the most deaths attributed to malaria in Sweden using the digitised and georeferenced data from Tabellverket. The numbers of cases occur in a specific area are shown on a spectrum of green to red. Areas with warmer tones (yellow-orange) indicate higher malaria-attributed

death density. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.