Exploring the Drivers of Malaria Elimination in Europe

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Exploring the Drivers of Malaria Elimination in Europe

by

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Specialisation: Environmental Modelling and Management

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Abstract

Malaria was once widespread in Europe, but during last century, malaria was eradicated from this continent and remained a highly stable state of elimination afterwards. The Global Malaria Eradication Project in the mid-20th century based on DDT spraying played a large part of freeing Europe from malaria, but it cannot explain the natural disappearance of malaria in certain regions of Europe before DDT became available. Moreover, despite the existence of competent vectors, large numbers of imported cases and the relaxation of control measures, the 'sticky' stability of malaria elimination in Europe seems to contradict the standard malaria transmission theory and vector control. Other factors, such as urbanization, economic growth, healthcare improvement and land use change may also have played a role in the decline of malaria in Europe, but their effects have rarely been quantified.

In this study, data of candidate variables were combined with malaria endemicity status at regional, national and individual country scales. Spatial and temporal comparisons were conducted to examine the correlations between malaria recession and variable changes. In addition, European countries were compared with current eliminating countries to assess the stages eliminating countries have arrived to.

The findings show that the socio-economic factors, such as increased wealth, healthcare improvement and increased urbanization which have been studied here, seem to have great effects on the elimination of malaria in Europe. The comparisons with eliminating countries indicate that eliminating countries have arrived the similar levels of socio-economic development to Europe at the time that elimination was achieved, but the higher temperature and shorter winter periods in those countries may demand higher development to achieve the goal of elimination. Though the sensitivity of those factors to malaria is not clear, the continuous economic development and rapid urbanization in endemic countries will likely lead to further reduction of malaria in the future, along with direct interventions.

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1 Introduction

1.1 Motivation of the study

The geographical range of malaria has been greatly contracted since the beginning of last century. In 1900, malaria was prevalent in almost every country in the world (Feachem and Malaria Elimination Group [MEG], 2009), covering 53% of global land area and 77% of world population (Hay et al., 2004). Substantial human efforts were devoted to malaria control. Among them, the Global Malaria Eradication Project (GMEP) based on dichloro-diphenyl-trichloroethane (DDT) spraying during 1955-1969 had a significant effect on the decline of malaria – 37 countries successfully eliminated malaria and many others greatly reduced the level of endemicity (Roll Back Malaria Partership [RBMP], 2011). Nowadays, there are still 97 countries and territories with ongoing malaria transmission (World Health Organization [WHO], 2012), exposing about half of the world`s population under the risk of this disease (Hay et al., 2004). The renewed interest in eradicating malaria (Roberts & Enserink, 2007) had greatly motivated current endemic countries that 34 of them are aiming to eliminate malaria and the rest are intensively controlling (MEG, 2012).

The continent of Europe was declared free of malaria transmission by WHO in 1975 (Bruce-Chwatt & de Zulueta, 1980). The anti-malaria activities based on DDT use were widely known to have played a great part in malaria elimination. But before the introduction of DDT, malaria was already spontaneously declining in certain regions of Europe (Hackett & Missiroli, 1930). Moreover, after the achievement of elimination in this continent, despite the existence of competent vectors, the increasing number of imported cases and the absence of interventions, secondary transmission and local outbreaks have remained rare, indicating a ‘sticky’ stability of malaria elimination (Chiyaka et al., 2013; Smith et al., 2013). This phenomenon seems to conflict with the standard theory of malaria transmission. Understanding the reasons behind would be of great value to current elimination programs.

Factors affecting malaria transmission were widely discussed in general and in specific Europe, such as climate, urbanization, wealth, healthcare system and land use change. Those factors might differ in the baseline of malaria transmission and change over time. Therefore to quantitatively identify the drivers of malaria elimination in Europe is to examine the associations between malaria endemicity and candidate drivers in both space and time. Exploring the main drivers of malaria elimination in Europe might provide valuable information to current endemic countries.

1.2 Research objectives

During this study, data of malaria endemicity and candidate drivers was extensively searched, and a strategy of three geographical-scale (regional, national and individual country scales) comparisons was developed. In order to assess the stages of current eliminating countries to elimination, current eliminating countries were compared with Europe at different levels of malaria endemicity. The general and specific objectives are stated as bellows.

1.2.1 General objective

To quantitatively identify the main drivers of malaria elimination in Europe and compare the differences in candidate drivers between European countries and current malaria eliminating countries.

1.2.2 Specific objectives

1. To compare the differences of candidate drivers in malarious and non-malarious areas, as well as the changes from malaria endemic to elimination at a regional scale.

2. To compare the changes in candidate drivers at the time of 1900, malaria with large drop and malaria eliminated at a national scale.

3. To examine the correlations among variables by the use of principle component analysis.

4. To compare the differences and changes in candidate drivers in individual countries.

5. To compare the differences in variables between European countries at different stages of endemicity and current malaria eliminating countries in 1900 and present time.

1.2.3 Research questions

Objective 1

- Which variables were associated with the elimination of malaria in Europe?
- What were the differences between spatial and temporal comparisons?

Objective 2

- Which variables had consistently changed along with the reduction of malaria in European countries?

Objective 3

- Which variables were correlated?
- Did the correlations among variables change by time?

Objective 4

- What were the main drivers of malaria elimination in individual countries?
- Were the main drivers different from country to country?

Objective 5

- Were European countries and current malaria eliminating countries different in 1900?
- How close were current eliminating countries to European countries at the time of malaria with large drop and that malaria eliminated?

2 Literature review

In this chapter, the background information related to this topic was reviewed. The first section explained the transmission cycle of malaria as a vector-borne disease, followed by the introduction of general factors affecting malaria transmission. Another three sections reviewed the control measures, the past and present elimination efforts. After that, the stability of malaria elimination in post-elimination countries was described. The last part concentrated on the historical malaria elimination in Europe.

2.1 Malaria transmission

Natural transmission of malaria involves of humans, vectors and parasites (Figure 1). Humans can get infected with malaria parasites through the bites of female Anopheles mosquitoes. Then the parasites start to reproduce through multiplication in the liver and this can cause the enlarged liver (White et al., 2014). After the asexual stage, the parasites travel to the bloodstream and affect the red blood cells, which in turn, can cause anopheles females to be pathogenic if they suck the infected blood. In this way malaria transmission cycle is established and recycled between humans and mosquitoes (Knell, 1991).

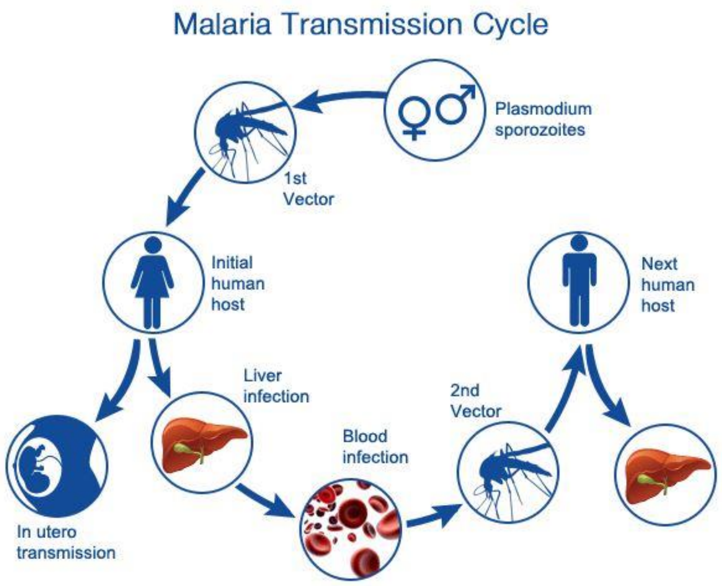


Figure 1. Malaria Transmission Cycle. Replicated from Euroclinix (http://www.euroclinix.co.uk/malaria-transmission.html)

The diversity of vectors, parasites and humans complicates the transmission cycle. Hundreds of species of mosquitoes exist in the world, among them about 70 are capable of transmitting malaria parasites (Service & Townson, 2002) and 41 are categorized as the dominant vector species (DVS) (Hay et al., 2010). DVS vary in spatial distribution (Figure 2) and differ in living behaviours, such as biting preference, larval inhabitants, adaptability to environment (Sinka et al., 2011; Sinka et al., 2010; Sinka et al., 2010). Those differences can affect the efficiency of malaria transmission. In terms of parasites, four species of malaria parasites are able to infect humans, all belonging to the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, (WHO, 2014). Among them, *P. falciparum* and *P. vivax* are the most common species. *P. falciparum* is the most deadly one (WHO, 2013), with the dominance in Africa (Gething et al., 2011; Hay et al., 2009) (Figure 3); and *P. vivax* is the most widely distributed species, mainly in Asia and Americas (Gething et al., 2012; Guerra et al., 2010) (Figure 4). Due to the ability to stay dormant in the liver for some months or even years, *P. vivax* parasites can survive in cold regions and also pose challenges for

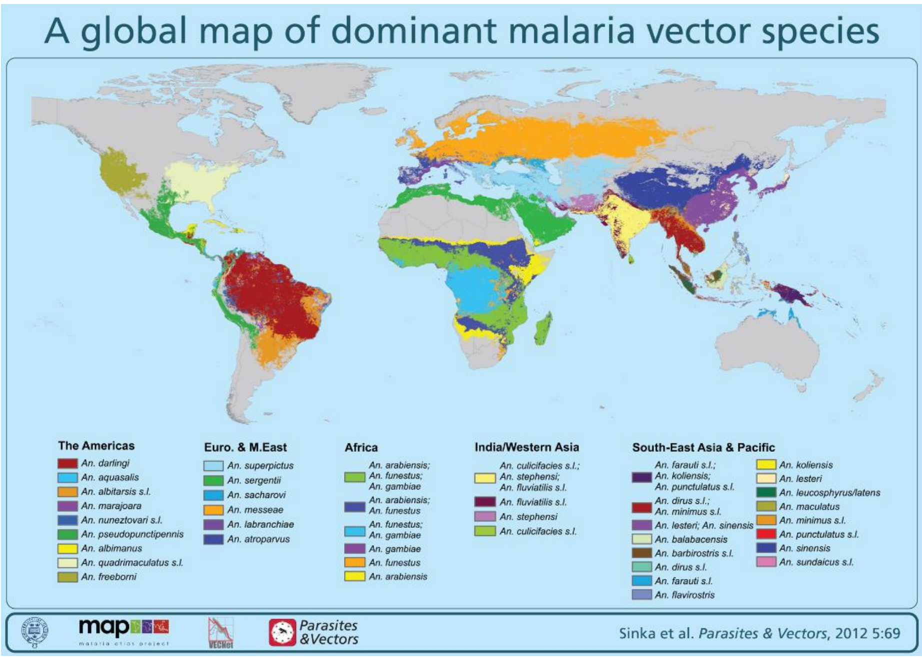


Figure 2. A global map of dominant malaria vector species (DVS). Downloaded from the Malaria Atlas Project (http://www.map.ox.ac.uk)

detection (Bruce-Chwatt et al, 1974; Faust, 1945). From the perspective of humans, children under five-year old and pregnant women are most susceptible. Besides, African populations are largely refractory to *P.vivax* infection because of the existence of Duffy negativity in their genes (Gething et al., 2012). In recent years, human movements to and from endemic areas expanded the spatial extent of malaria infections and made transmission dynamic (Tatem et al., 2006; Tatem & Smith, 2010).

Apart from the natural transmission by female mosquitoes, malaria can also be transmitted through blood transfusion (Bruce-Chwatt, 1974), organ transplant (Machado et al., 2009), or the shared use of needles or syringes due to the parasites being lodged in the red blood cells. However, those cases are very rare comparing with mosquito transmitted malaria.

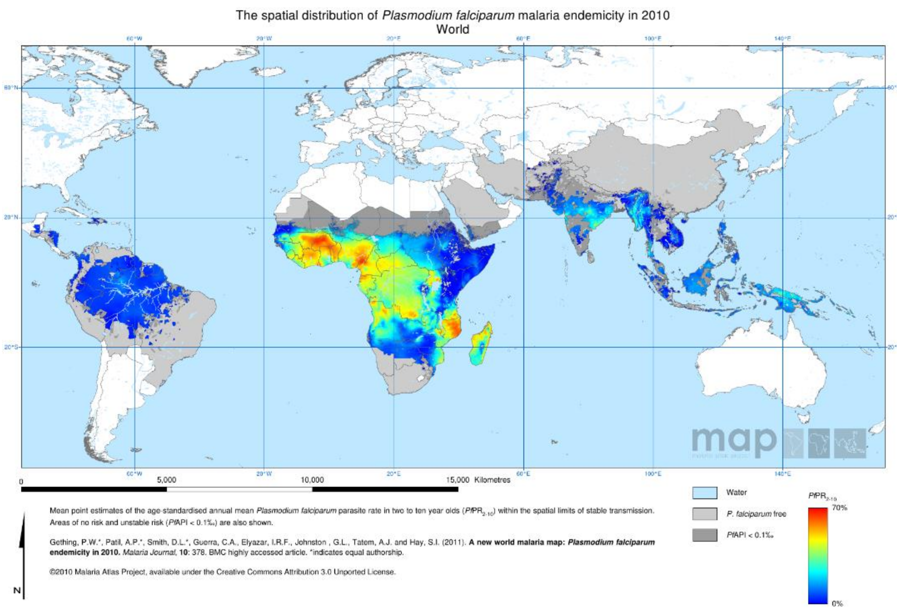


Figure 3. The spatial distribution of *Plasmodium falciparum* malaria endemic in 2010 World. Downloaded from the Malaria Atlas Project (http://www.map.ox.ac.uk.)

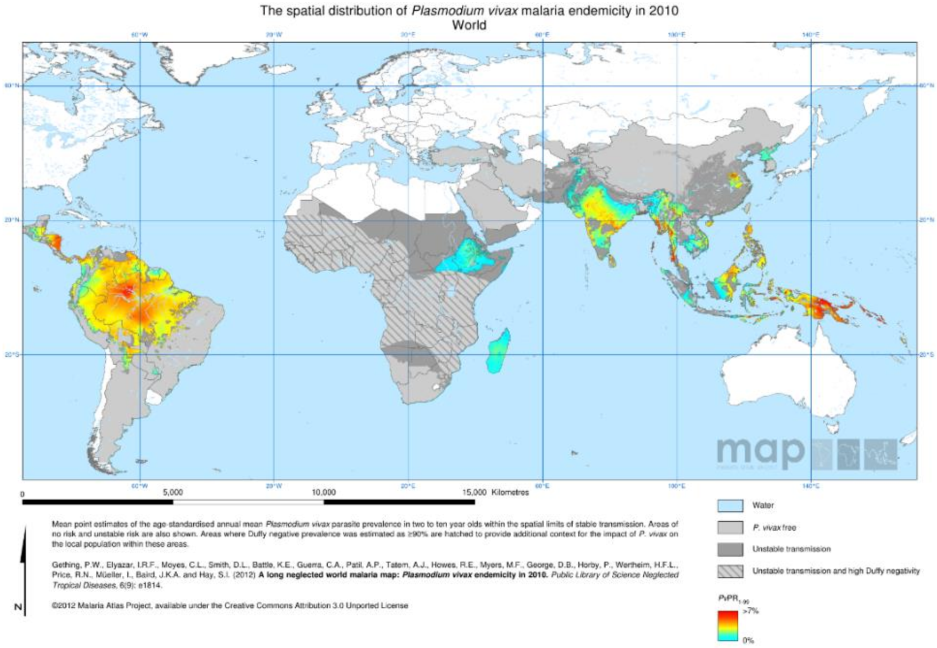


Figure 4. Spatial distribution of *Plasmodium vivax* malaria endemic in 2010 World. Downloaded from the Malaria Atlas Project (http://www.map.ox.ac.uk).

2.2 Factors affecting transmission

In general, factors of climate, urbanization, wealth and healthcare system have been discussed to have considerable effects on malaria transmission.

2.2.1 Climate

Climatic variables, especially temperature and precipitation, are commonly known factors affecting malaria transmission. Temperature influences mosquito distribution, feeding intervals and lifespan, as well as the rate of parasite multiplication in female mosquitoes (Macdonald, 1957; Reiter, 2014; WHO, 1962). The obvious evidence seen was that malaria recession started from the coldest zones and gradually constrained itself to tropical regions (Hay et al., 2004). The role of rainfall in promoting malaria transmission is mainly by creating breeding sites for mosquito reproduction (Martens et al, 1995; Reiter, 2014). Besides, rainfall can also increase atmospheric humidity, which affects the internal water balance of mosquitoes and thus reduces their longevity (Benali et al., 2014). In 1953, the malaria epidemic in Ethiopia was coincident with the long-period rainfall, and the increased temperature and humanity (Fontaine et al, 1961). However, heavy rains can destroy the breeding sites and result in malaria decline (Martens et al, 1995; Reiter, 2014). Beyond those, transmission also reveals seasonal patterns. In temperate zones, seasonality affects the living habits of mosquitoes, which further influences the patterns of malaria transmission (de Buck et al., 1927). In tropical regions, the character of malaria transmission varies in the rain and dry seasons (Craig et al, 1999).

The global warming pattern in the past centuries aroused substantial concerns about the potential increases in the endemicity of vector-borne diseases (Campbell-lendrum et al, 2015; Reiter, 2001; Shuman, 2011), in particular malaria (Hay et al., 2002; Martens et al., 1999; Martens et al., 1997). Rising temperature affects pathogen maturation and replication within mosquitoes, as well as vector reproduction, thus increases the likelihood of malaria infection (Costello et al., 2009). But the temperature change might not be the dominant factor affecting malaria transmission, as malaria decline in last century was concurrent with the global warming phrase, also because malaria was seen to have transmitted in cold period (Reiter, 2000). Gething et al. (2010) found that non-climatic factors had larger effects on interrupting malaria transmission than the potential increases of malaria infections caused by climate change, so that the effects from the climate change could be offset by other factors.

2.2.2 Urbanization

Nowadays, roughly half of world population live in urban settlements, and this proportion was projected to reach 66% by 2050 (United Nations [UN], 2014). The rapid increases in urbanization had great impacts on the epidemiology of malaria. A number of studies showed urban areas sustain less malaria endemicity than their rural counterparts (Hay et al., 2005; Qi et al., 2012; Tatem et al., 2013). Reasons for this were discussed. The process of urbanization reduces the open spaces for mosquito breeding, and the remaining water bodies have great potential to be polluted. Reduced breeding sites helps decrease the vector population. From the human aspect, the high population density in cities disperses the infected bites per person receives, so urban dwellers have less chances to get infected with malaria (Robert et al., 2003; Smith et al., 2004). In addition, urban population benefit from higher living standards, including better access to healthcare facilities and treatment (Hay et al., 2005), improved nutritious and health status, better housing quality and so on. Those help better separate humans from mosquitoes and improve human immunity to diseases.

2.2.3 Wealth

The wealth of a country indirectly affects the transmission of malaria. For endemic countries, malaria control requires large amounts of financial support (Sabot et al., 2010). Countries with high incomes tend to have more resources at their disposal and thus make malaria elimination and the subsequent maintenance easier. Also wealthier countries are likely to have higher urbanization, better living environments, better healthcare system and better nutritious conditions and so on. Feachem et al. (2010) reviewed 99 countries that attempted to eliminate malaria and results showed that countries successfully eliminated malaria had higher GDP per head than those failed.

2.3 Controlling malaria

Despite factors that affect malaria transmission, purposive interventions had great contribution to malaria reduction as well. The main concepts of controlling malaria can be generalized as attacking mosquitoes, reducing contacts between humans and mosquitoes as well as treating infected humans. Traditional malaria control was focused on marsh drainage and larval control, to destroy mosquito breeding sites (James, 1929; Majori, 2012). Drugs for malaria treatment were limited to quinine (Dobson, 1980; Majori, 2012). In 1945, the use of indoor residual spraying (IRS) with DDT proved to be efficient in attacking adult mosquitoes, so it soon became the most popular method to control malaria (Russell, 1957). However, the emergence of insecticide resistance or reduced effectiveness of insecticides and the parasite resistance towards quinine in many areas partially resulted in the failure of eradicating malaria (Wright et al, 1972). New approaches for malaria control were explored, such as larvivorous fish and genetic manipulation, but those had limited application and success (Wright et al, 1972). Only from recent decades, some new techniques, such as insecticide-treated nets (ITNs), artemisinin-based combination therapy (ACTs) and rapid diagnostic tests (RDTs) were developed and became common tools for controlling malaria (Figure 5).

Today, an integrated malaria control strategy has been established and commonly used, that is, vector control through ITNs and IRS, preventing pregnant women and young children in particular by chemoprevention, detection with microscopy and RDTs, malaria treatment primarily by ACTs with chloroquine and primaquine as supplements (WHO, 2014).

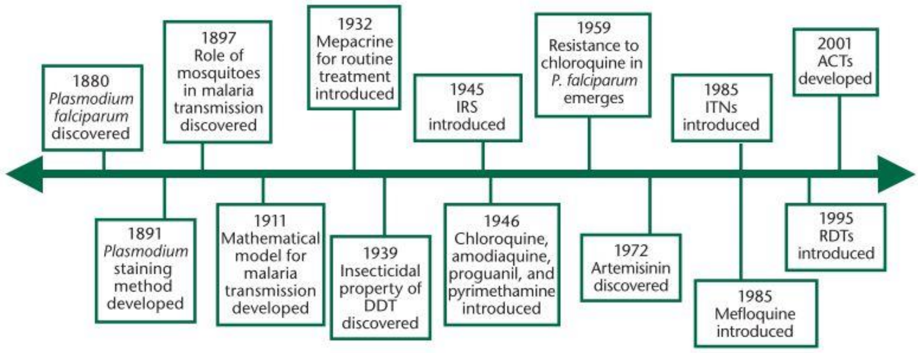


Figure 5. Timeline of the development of the malaria armamentarium. Replicated from the Global Health Group (2009).

2.4 Past elimination efforts

Malaria elimination, eradication and control are frequently used concepts. Those three terms are all about the reduction of malaria infections. But Malaria elimination refers to "a state where interventions have interrupted endemic transmission and limited onward transmission from imported infections below a threshold at which risk of reestablishment is minimized. Both capacity and commitment to sustain this state indefinitely are required" (Cohen et al., 2010). Malaria eradication is "malaria elimination at a global level" (Chiyaka et al., 2013). Malaria control is the intervention of malaria when elimination is currently not feasible, defined by WHO as "reducing the disease burden to a level at which it is no longer a public health problem" (WHO, 2008).

Early human efforts of malaria control based on water drainage and quinine distribution achieved some progresses in many countries, such as UK (James, 1929), US (Faust, 1945), Italy (Majori, 2012) and Venezuela (Griffing et al., 2014). With the advent of DDT, national goals of eliminating malaria were initially set up in Venezuela, Italy, Ceylon (Russell, 1957) and US (CDC). Those programs achieved unprecedented successes, therefore in 1955, WHO launched the Global Malaria Eradication Project (GMEP), aiming to eradicate malaria (Macdonald, 1965; Russell, 1957). Most countries joined this campaign expect African regions, due to some technical, financial and political obstacles (Nájera et al, 2011). This program was based on the Ross-Macdonald theory of mosquito-borne pathogen (Smith et al., 2012), including four phases: preparatory, attack, consolidation and maintenance (Russell, 1957). It achieved great successes that 37 of the 143 participated countries eliminated malaria, including two continents: Europe and Australia, with the rest of countries experiencing striking malaria decline (RBMP, 2011; Wright et al., 1972). However, due to the resistance of parasite to medicine and mosquito towards insecticides as well as the shrinkage of financial support, the goal of eradication was recognized as being infeasible at that time, GMEP collapsed in 1969 (Nájera et al., 2011; WHO, 1969). After that, the responsibility of eliminating malaria was taken over by individual countries and little progress was made (MEG, 2009).

In total, malaria endemic areas had been significantly contracted during the 20th century, as shown in Figure 6.

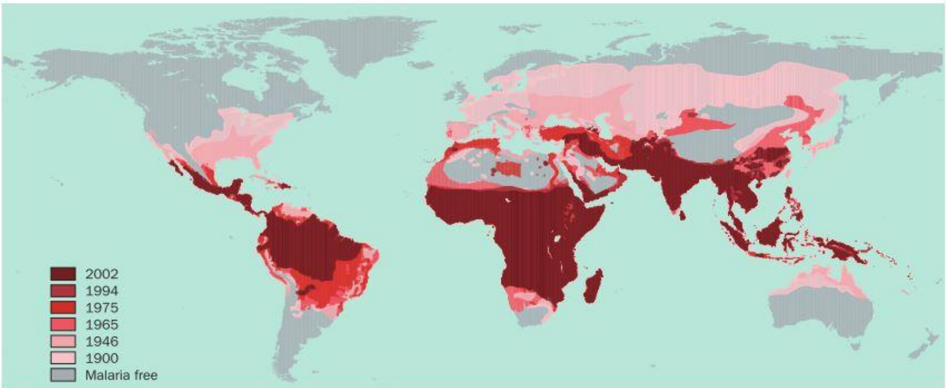


Figure 6. All-cause global malaria distribution maps for preintervention distribution (circa 1900) and for the years of 1946, 1965, 1975, 1992, 1994 and 2002. Replicated from Hay et al. (2004).

2.5 Present elimination efforts

2.5.1 Scale-up interventions

Malaria elimination has drew renewed interest in recent years. In 1998, the Roll Back Malaria (RBM) Partnership was launched to implement coordinated action against malaria (RBM, 2014). More funding opportunities, especially the Global Fund to Fight AIDS, Tuberculosis and Malaria (Feachem & Sabot, 2006), made the scale-up of control activities possible. In 2007, Bill and Melinda Gates´ call for eradiating malaria reoriented the goal of malaria elimination (Roberts & Enserink, 2007). Following that, RBM partnership set up Global Malaria Action Plan (GMAP) (RBMP, 2008), providing strategies at global and regional scales, with the aim of reducing malaria burden in the near future. Subsequently, the malaria elimination group (MEG) emerged a three-part strategy to progressively reach malaria eradication (MEG, 2009a, 2009b): (1) aggressive control in high-risk malaria countries, to achieve low transmission and mortality in countries currently experiencing the highest burden of disease and death; (2) progressive elimination from the endemic margins, to shrink the malaria map; (3) research into improved vaccines, drugs, diagnostics, insecticides, and other tools.

The three-part strategy has been further developed. To specify aggressive control and progressive elimination, Feachem et al (2010) introduced the new term of controlled low-endemic malaria, which is defined as "a state where interventions have reduced endemic malaria transmission to such low levels that it does not constitute a major public health burden, but at which transmission would continue to occur even in the absence of importation". On the other hand, a malaria-eliminating country refers to "a country in the process of moving from controlled low-endemic malaria towards elimination". consisting of two categories: countries has formally declared or is strongly considering evidence-based national elimination goal (Feachem et al., 2010). Nowadays, 34 of 97 endemic countries are considered as malaria-eliminating countries (MEG, 2015), and the rest 63 countries are controlling malaria. When countries consider moving from control to elimination, a feasibility assessment was recommended (Feachem et al., 2010), as trailed in Zanzibar (Moonen et al., 2010). For strategy part three, a research agenda (malERA, 2011) was developed to break the knowledge gaps in reducing malaria mortality and morbidity.

2.5.2 Recent successes

The scaling-up of malaria interventions in recent years has made encouraging achievements (WHO, 2014). During the period of 2000 to 2013, five endemic countries were certificated as malaria-free, which were Kazakhstan, the United Arab Emirates, Morocco, Turkmenistan and Armenia (RBMP, 2011). Additional six countries stepped into the phase of prevention of reintroduction (WHO, 2014b). Moreover, malaria cases had been reduced by 30% globally and 34% in the WHO African Region, which resulted in larger declines in malaria death rates, which were 47% worldwide and 54% in Africa.

2.5.3 Importation risk

Imported malaria cases through human and vector movements (Stoddard et al., 2009; Tatem et al., 2006) are getting increasingly important. As a result of unprecedentedly dynamic human movements (Pindolia et al., 2014) and advanced transportation tools especially air travel (Huang & Tatem, 2013; Tatem et al, 2006), imported malaria infections are higher than any time in history. This trend does not only put malaria-free countries under the risk of sporadic outbreaks, which were seen in US (CDC, 2002, 2003) and Greece (Danis et al., 2013); but also destroys the progresses made in eliminating countries. A typical example can be seen in Zanzibar. The local malaria transmission there had been very low, but the continuous imported infections from neighbouring highly endemic countries took up even more proportion of total malaria cases, making elimination an unachievable goal (Le Menach et al., 2011).

2.6 The stability of malaria elimination

Post-elimination countries were found to exhibit a 'sticky' stability of malaria elimination (Chiyaka et al., 2013; Smith et al., 2013). Between 1945 and 2010, 79 countries eliminated malaria successfully and 75 of them remained malaria free (Feachem et al., 2010). In contrast, a review of malaria resurgence (Cohen et al., 2012) identified 75 resurgence events in 61 countries, where local transmission was once sustained through anthropogenic interventions but not yet eliminated. In those 61 countries, apart from 4 countries eliminated malaria in a later time, the rest were still endemic. Those facts suggest a stable state of malaria elimination (Smith et al., 2013).

The stability of malaria elimination was also explained quantitatively by the reproductive numbers (Le Menach et al., 2011; WHO, 1966). The basic reproductive number, R_o, represents "the expected number of human cases that would rise from a single introduced malaria case in a population with no immunity and no control" (Smith et al., 2009). R_o measures the maximum potential transmission (Tatem et al., 2010). With various forms of interventions, *Ro* will be termed to the reproductive number under control, that is, R_c (Smith et al., 2009). The lower the value of R_c, the less potential of the disease prevalence. When R_o or R_c is lower than 1, transmission will decline and in the end be interrupted (Farrington et al., 2003). Based on the branching process proposed by Cohen et al (2010), Chiyaka et al (2013) calculated R_c in 30 post-elimination countries. Results showed that the overall yearly average R_c was approximately 0.04, with about 85% year-by-country less than 0.01.

By theory, those low R_c values indicate the high level of interventions. But in fact, no intentional control measure was taken in place in those post-elimination countries. A possible explanation for this might be that other forces or factors were having an effect equivalent to or even stronger than interventions, so that the receptivity of malaria (WHO, 1966) in those countries stayed very low.

2.7 Malaria elimination in Europe

Malaria was once prevalent in Europe. In the second half of the 19th century, spontaneous decline of malaria started in UK (Kuhn et al., 2003) and certain regions of mainland Europe, referred to as "anophelism without malaria" (Hackett & Missiroli, 1930). During 20th century, malaria in Europe had seen several rises and falls (Figure 7), mainly attributed to the First and Second World Wars (Bruce-Chwatt & De Zulueta, 1980). The final elimination of malaria started from the end of the Second World War, progressively from the Northern part of Europe to the Southern part. Until 1975, the continent of Europe was declared free of malaria transmission (Bruce-Chwatt & De Zulueta, 1980). Afterwards, aside from occasional sporadic malaria cases (Danis et al., 2013), the risk of malaria resurgence in European countries was very low, showing a stable state of malaria elimination.

Causes for the recession of malaria in Europe were studied by country or region, and those can be divided into two categories: the early natural disappearance of malaria and later intentional interventions.

For UK, James (1929) considered each factor that might have influenced the disappearance of malaria and came to the conclusion that "the diminution of local malaria in England was due neither to natural causes nor to the intentional application of any particular preventive method reputed to be specific, but to progressive improvements of a social, economic, educational, medical and public health character". Dobson (1980) suggested that the reduction of malaria in UK were due to a series of changes, such as marsh drainage and reclamation, introduction of new root crops, vectors preference of cattle to humans, improvement in housing, better access to cinchona bark and quinine, and improved health or nutritional status and so on. Kuhn et al. (2003) used a regression model to examine the relationships between malaria cases and variables, and found that inland water coverage, mean temperature and total precipitation had positive associations with malaria death rates, while cattle density had a negative effect.

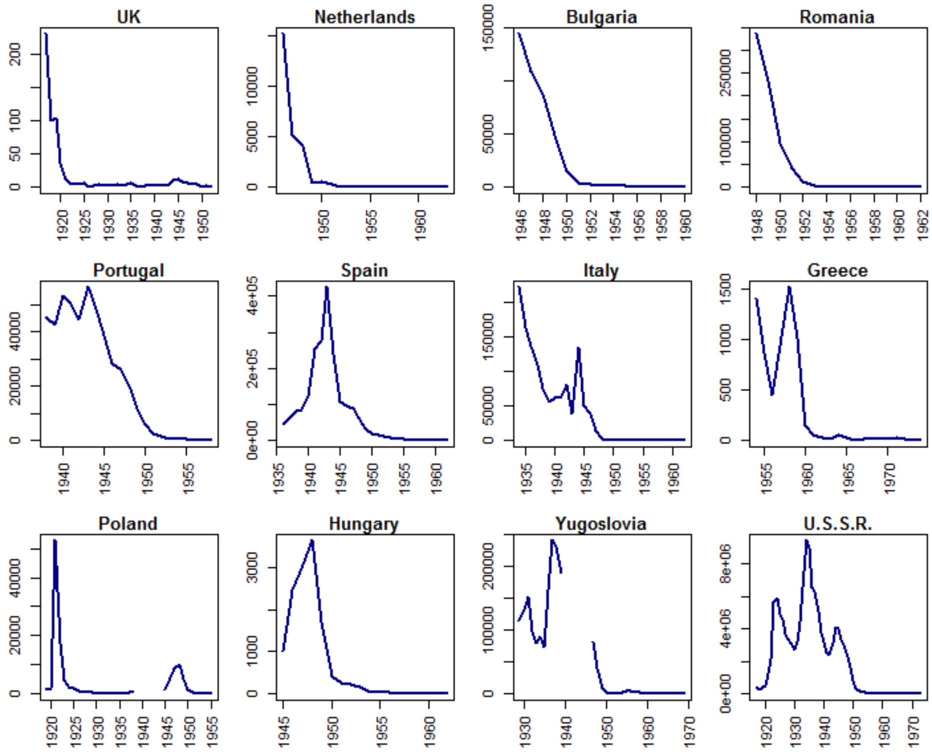


Figure 7. Plots showing the ups and downs of malaria case numbers in some European countries. The case numbers for UK and the Netherlands were indigenous ones and those for other countries were overall cases.

In mainland Europe, cases differed from country to country. In Denmark, evidences were found that anophelines became no longer interested into human blood, but confined themselves to domestic animals (Bruce-Chwatt & de Zulueta, 1980; Hackett & Missiroli, 1930). Roubaud (1920, cited in Hackett & Missiroli, 1930) proposed that the cause of this was the natural selection that created the zoophile race of mosquito. But Wesenbuhg-Lund (1920, cited in Hackett & Missiroli, 1930) believed that it was the coldness of the climate that forced anophelines to choose the warm stables instead of emptier human bedrooms. In the Netherlands, de Buck et al.(1927) compared the two anopheline species in malarious and non-malaria regions. The species in non-malaria regions was found to hibernate earlier and became inactive in malaria transmission months. Malaria in Finland was shown to be not affected by the cold temperature, but more like an "indoor" disease (Hulden et al., 2005). The reduction of malaria proved to be highly linked to the decreasing household size and improved housing standard (Hulden & Hulden, 2009).

Apart from the natural disappearance of malaria, most European countries had conducted nationwide anti-malaria activities, mainly by intensive use of DDT spaying. The start dates of control activities, the dates of the last indigenous cases and that WHO certificated or added as malaria-free countries are shown in Appendix. As can be seen, most anti-malaria activities were taken during 1940s and 1950s, and the last cases of malaria were mostly reported in 1950s and 1960s.

Clearly, human interventions had greatly contributed to malaria elimination in Europe. But those activities cannot explain the natural disappearance of malaria, nor the 'sticky' stability of elimination when control measures were out of place and imported infections were continued. Factors related to malaria transmission were proposed in general and in Europe, but not quantified.

3 Methodology

3.1 Overview of methodology

The main purpose of data analysis in this study was to find the relationships between malaria endemicity and candidate variables. Candidate variables in both spatial and temporal dimensions were compared. Considering that the driving forces might have different effects at different geographical scales, three scales of comparisons in Europe were designed – regional comparisons, national comparisons and individual country case studies. In addition, correlations among variables were analysed at the national scale. In the end, 34 current eliminating countries were compared with Europe at different levels of malaria endemicity in last century. Figure 8 displays the whole structure of methodology used in this study.

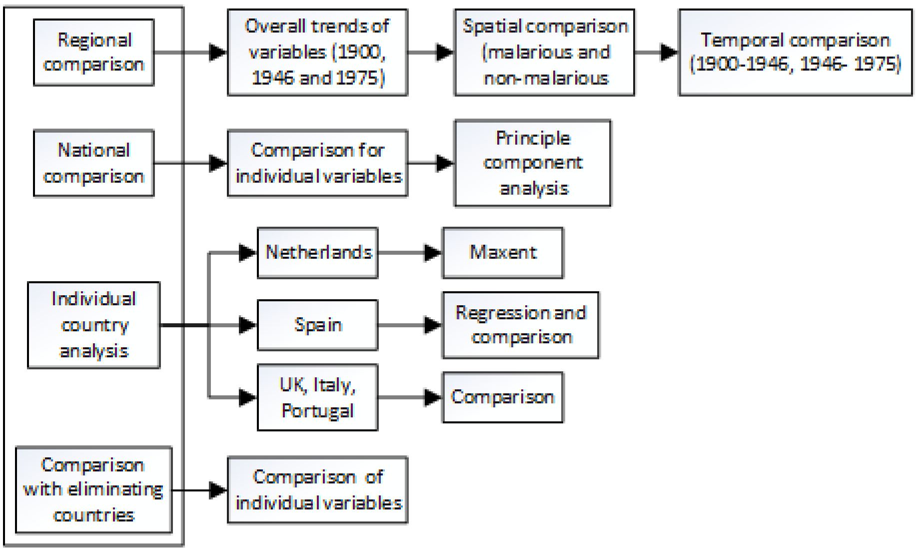


Figure 8. The structure of data analysis for the whole project.

At the regional scale, the overall trends, spatial differences in malarious and non-malaria areas, and temporal changes from endemicity to elimination were studied. The overall comparisons of variables present the general trends of changes in Europe. Spatially, based on the extracted malaria maps from Figure 6 in 1900 and 1946, endemic and malaria-free areas were compared. Temporally, areas that eliminated malaria from 1900 to 1946 and from 1946 to 1975 were compared. Climate data was studied monthly to see the seasonal variations, while urbanization and land use variables were calculated to percentages.

At the national scale, countries were compared at three time points, that is, 1900, malaria with large drop and malaria eliminated. The latter two time points were determined by Figure 7 and Appendix, complimented by literature review. Thus national-scale comparisons were only about changes with the reduction of malaria. The global malaria maps (Figure 6) were not used here because the accuracy was not sufficient at the national scale. Principle component analysis (PCA) was performed to detect the correlations among variables.

Five individual countries were studied in more detail, which were the Netherlands, Spain, Italy, Portugal and Britain. Different approaches were used depending on the format of endemicity data. Specifically, for point malaria occurrence data in the Netherlands, Maxent was used; for provincial case numbers in Spain, forward and backward regression and comparisons were carried out; and for malaria endemicity maps in Italy, Portugal and Britain, the spatial differences and temporal changes based on malaria endemicity were compared.

Finally, European countries at the time of 1900, malaria with large drop and malaria eliminated were compared with current malaria eliminating countries in 1900 and contemporary time.

For comparisons that differences or changes of groups could not be clearly visualized, an appropriate statistical test was conducted to determine if they were significantly different.

3.2 Study sites

The study sites consist of three parts: 31 European countries, 5 individual European countries and 34 current malaria eliminating countries. 31 European countries were selected from the continent of Europe, for regional and national comparison. Then the study site focused on 5 individual countries where malaria endemicity data exist. The last study site was the 34 current malaria eliminating countries, which were to compare with those 31 European countries.

3.2.1 European countries

The continent of Europe is located in the northern hemisphere, defined by 34°48'02" N to 81°48'24" N and 31°16'30" W to 69°02' E. It is composed of 50 countries. This study focuses on 31 large European countries where malaria was eliminated during the period of 1900 to 1975 (Figure 9). Countries such as Iceland, Ireland, Norway, Sweden and Switzerland either never had malaria transmission or eliminated malaria before 1900, and therefore, were excluded from the study area. Though Denmark was officially recognized as being malaria-free in 1950, literature (Bruce-Chwatt & De Zulueta, 1980; Paul Reiter, 2001) shows that there had been no indigenous malaria cases since the start of 20th century, so in this study Denmark was removed from the study site as well. Besides, due to the relatively coarse resolution of available spatial datasets, small countries and some islands were not included in the study site.

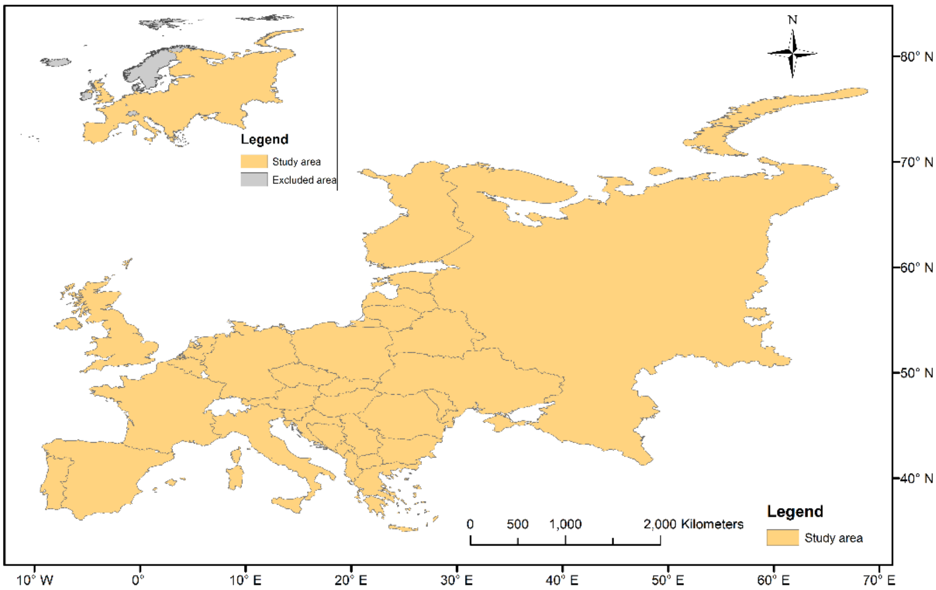


Figure 9. Study site of 31 European countries.

3.2.2 Individual country studies

To determine which factors contributed to the elimination of malaria at a smaller scale, malaria endemicity information were searched in each of 31 studied European countries. In the end endemicity data were found in 5 countries: Spain, the Netherlands, Italy, Portugal and Britain, as highlighted in Figure 10.

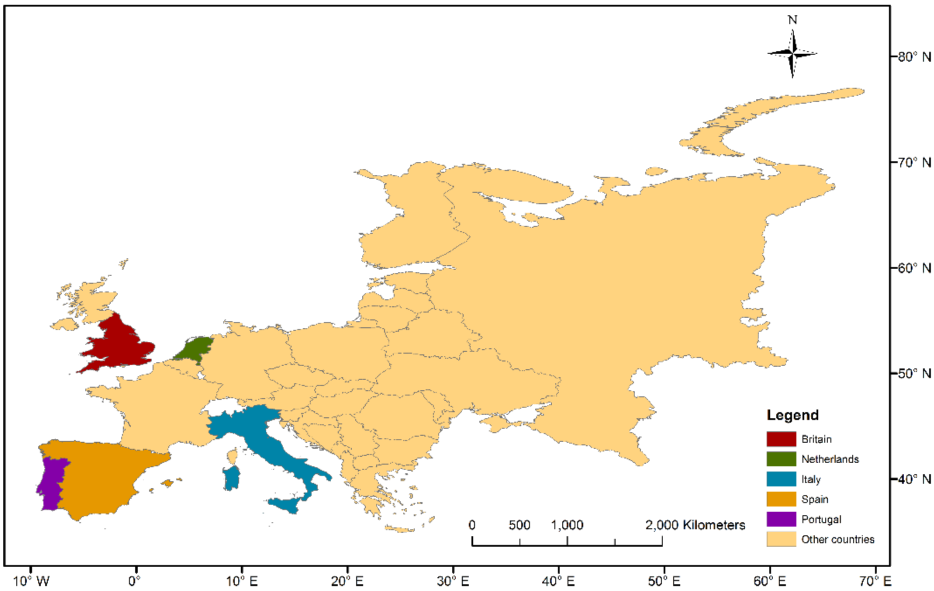


Figure 10. Study site of 5 individual European countries.

3.2.3 Current eliminating countries

The third study site is the 34 current malaria eliminating countries, as shown in Figure 11 in blue colour. Those were used for the comparisons with post-elimination European countries. As those countries are located in different continents, there are a wide range of variations in climate, socio-economic conditions and so on.

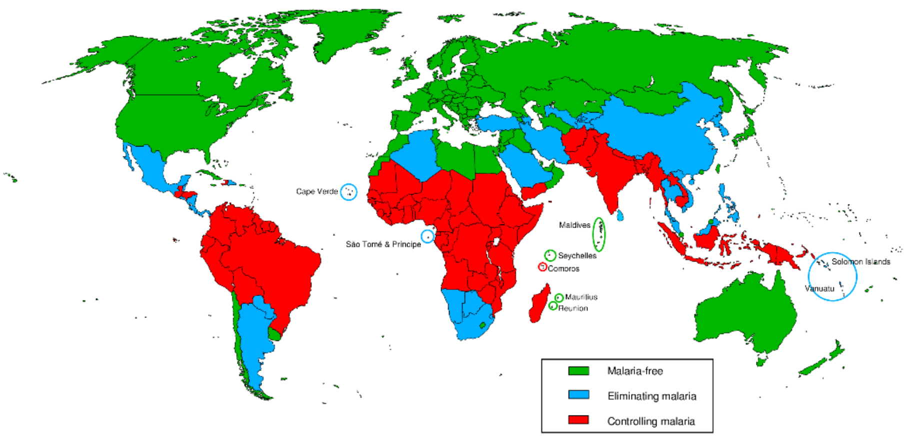


Figure 11. Categorisation of countries as malaria-free, eliminating malaria and controlling malaria, 2012. Countries in blue colour are

eliminating malaria and also are the third study site in this study. Figure replicated from MEG (http://www.malariaeliminationgroup.org/resources/elimination-countries).

3.3 Materials

Two types of data were needed for data analysis. One was the variable datasets, and the other was the malaria endemicity data. Both were extensively searched. In the end, variable data was obtained from various sources and historical malaria endemicity information was mainly found in literature.

3.2.1 Candidate drivers

The selection of candidate drivers was based on both literature review and available data sources. Results consist of climatic variables (temperature, precipitation and frost day frequency), GDP per capita, life expectancy, urbanization (urban area and urban population) and land use change (cropland and grassland). Among them, variables of GDP per capita and life expectancy were aggregated national datasets, so they cannot be used for regional comparisons and individual country studies. The rest of variables were in raster format.

3.2.1.1 Climatic variables

Climatic Research Unit (CRU) TS (time-series) datasets v3.10 (http://www.cgiar-csi.org/data) are monthly gridded data covering the period from 1901 to 2009, with a resolution of 0.5×0.5 degree. The calculation of those datasets were based on an archive of monthly mean temperature collected from more than 4000 weather stations all over the world. Different climatic variables are available. For malaria transmission, three most related variables were chosen for analysis, which were mean temperature, precipitation and frost day frequency. Temperature and precipitation were widely known to be related to malaria transmission. Frost day frequency roughly indicates the length of winter breaks that mosquitoes might hibernate or semi-hibernate, which means the capability of malaria transmission is potentially depressed. As the datasets are in ASCII format, all variables have a scaling factor of 10 or 100, therefore, the true estimated values should be obtained by the division of the corresponding scaling factors.

3.2.1.2 Urbanization, population and land use data

History Database of the Global Environment (HYDE) 3.1 (http://themasites.pbl.nl/tridion/en/themasites/hyde/) is a long-term dynamic modelling effort in estimation of some demographic and agricultural driving factors of global change (Goldewijk et al 2010; Goldewijk et al, 2011). It provides consistent gridded datasets. Factors involved are total population, urban population, cropland and grassland. Those datasets are in 5×5 minute raster format, available in the decades of the period from 1900 to 2000. The construction of HYDE database started from a new global map comprising 222 countries and 3441 administrative units (Klein Goldewijk, 2005). Historical population data were gathered from a variety of sources including foundational population data sources in country level (Denevan, 1992; Livi-Bacci, 2007; Maddison, 2001; McEvedy & Jones, 1978) and subnational data as supplement (Lahmeyer, 2004). Urban/rural fractions were obtained from the collection of the United Nations (UN, 2008) for the time after 1950. For that of pre-1950, multiple sources for individual countries were used or estimated. In the end, a model based on Gaussian probability density function was built to estimate population density and urban area at each decade (Goldewijk et al., 2010). For cropland and grassland, country level data for post-1961 period were derived from the Food and Agriculture Organization of the United Nations (FAO, 2008); pre-1961 data were estimated by per capita use and adjusted by time (Goldewijk et al., 2011). Then the spatial allocation of cropland and grassland were modelled by pre-defined criteria (Goldewijk et al., 2011).

Goldewijk & Verburg (2013) qualitatively assessed the magnitude of uncertainties in HYDE datasets. Results suggest that the HYDE datasets in Europe, North America and Australia have high certainties, but other regions have relatively low certainties. Besides, data in recent years are generally more reliable than that from early time. Nevertheless, considering the broad spatial scale and the main study area as Europe, the effects of uncertainties in the datasets are likely small.

3.2.1.3 GDP, life expectancy

Gross Domestic Product (GDP) per capita data and life expectancy data were obtained from Gapminder (http://www.gapminder.org/), which provides a range of demographical, socio-economic and health indicators. The latest vision of GDP dataset is based on fixed 2011 prices, adjusted for Purchasing Power Parities (PPPs) in international dollars (Gapminder, 2011). Life expectancy at birth is defined as “the average number of years a newborn child would live if current mortality patterns were to stay the same” (Gapminder, 2014). The variable of life expectancy represents the overall level of health system in each country.

The establishment of both datasets involved substantial estimations, assumptions and modelling. The construction of GDP per capita was based on relative growth rates and cross-country comparisons (Gapminder, 2011). And that of life expectancy consists of a crude baseline modelling and an estimation of improvements in health-transition (Gapminder, 2014).

All variables used are displayed in Table 1.

Table 1. Variables used for comparisons.

Variable	Format	Spatial resolution	Temporal resolution	Temporal frame	Source
Daily mean temperature	ASCII	0.5 degree	Monthly	1901~2009	CRU-TS v3.10
Perception	ASCII	0.5 degree	Monthly	1901~2009	CRU-TS v3.10
Frost day frequency	ASCII	0.5 degree	Monthly	1901~2009	CRU-TS v3.10
GDP per capita	Aggregated	National	Yearly	1800~2013	Gapminder
life expectancy	Aggregated	National	Yearly	1800~2013	Gapminder
Population	Raster	5 min	Decade	1900~2000	HYDE 3.1
Urban population	Raster	5 min	Decade	1900~2000	HYDE 3.1
Cropland	Raster	5 min	Decade	1900~2000	HYDE 3.1
Grassland	Raster	5 min	Decade	1900~2000	HYDE 3.1

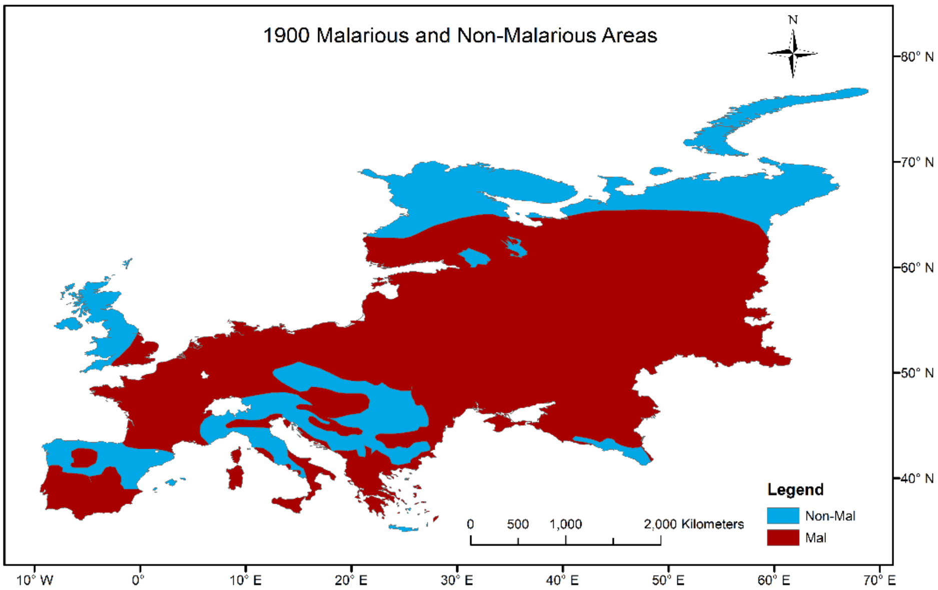
3.2.2 Malaria endemicity

Information of historical malaria endemicity in Europe provides the baseline of variable comparisons. Here, there are three types of endemicity data: malaria maps, dates of malaria decline and elimination, and malaria case numbers. Existing malaria maps were used for regional and individual country comparisons; dates of malaria decline and elimination defined the temporal segmentation of national comparisons, but those dates were partially determined by country case numbers; malaria morbidity and mortality data were used in Spain.

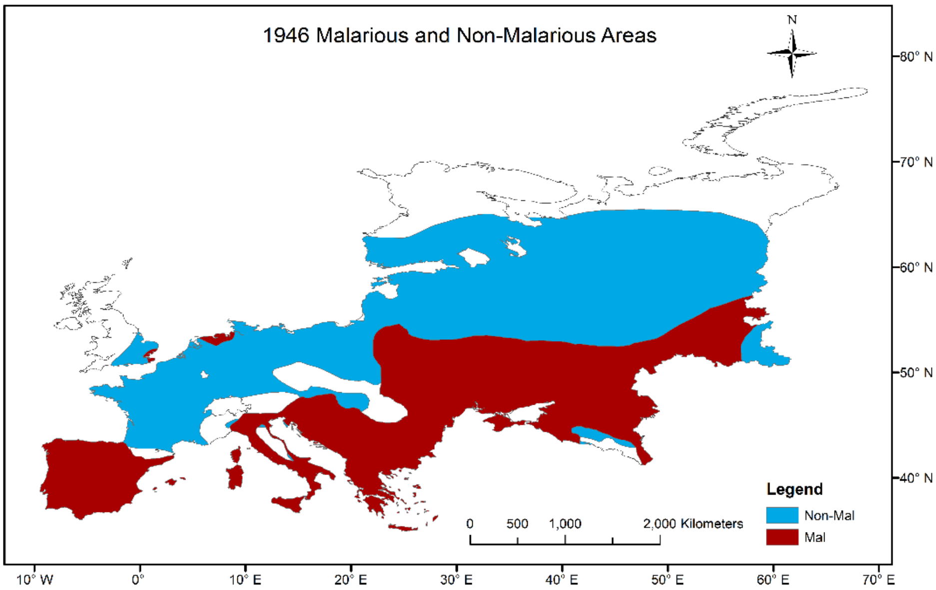
3.2.2.1 Regional malaria maps

Global malaria maps across last century were collected by Hay et al (2004) (Figure 6). The earliest map was developed by Lysenko & Semashko (1968, cited in Hay et al (2004)) at the time of near 1900. Massive data were searched from historical records, documents and maps for all *Plasmodium* species. Similarly, Hay et al (2004) compiled data from country reports and WHO regional offices for the production of malaria distribution maps in 1946, 1965, 1975, 1992, 1994 and 2002. In Europe, malaria endemic areas were shown in c.1900, 1946 and 1965. Considering HYDE datasets are only available in decade intervals and that malarious areas in 1965 Europe constituted only a small, therefore the 1965 malaria map was not used in this study.

For regional comparison, malaria maps in 31 European countries were derived from 1900 and 1946 global malaria maps, as shown in Figure 12 (a) and (b). The malarious and non-malaria regions in 1946 were merely extracted from the endemic part in 1900, excluding the malaria-free areas in 1900. Spatially, comparisons were based on malarious and non-malaria areas, in both 1900 and 1946. Temporally, comparisons were dependent on Figure 11 (b). The non-malaria region in this map eliminated malaria from 1900 to 1946, so variables for this area were compared between 1900 and 1946; and the still endemic zone became malaria-free by 1975 (as malaria was eradicated from Europe by 1975), so variables were compared for this area between 1946 and 1975.



(a)



(b)

Figure 12. Malaria maps for regional comparisons. (a) 1900 malarious and non-malaria areas in Europe; (b) 1946 malarious and non-malaria areas in Europe. The non-malaria area in 1946 map only shows the part that eliminated malaria from 1900, not the whole non-malaria area.

3.2.2.2 National malaria decline and elimination dates

At the national scale, three time points were set for variable comparisons, which were 1900, malaria with large drop and malaria eliminated. Information on the dates of malaria with large drop and malaria eliminated was mainly obtained from the book of 'the rise and fall of malaria in Europe: A historico-epidemiological study', wrote by Bruce-Chwatt & de Zulueta (1980). This was complemented by other literature and reports. The ups and downs of malaria in most countries were visualized in Figure 7. The dates of malaria elimination were defined by the records of last indigenous cases and the dates that countries were certificated or added as malaria-free countries by WHO, as collected in Appendix. All dates were set in decade interval with consideration that HYDE datasets were available only in decades and also that the temporal delineation on malaria reduction was relatively crude. Depending on those sources, the dates of the three time points at national scale were defined, as displayed in Table 2.

Table 2. Dates of three time points for national comparison in 31 European countries: start year, malaria with large drop and malaria eliminated.

Country	Start year	Malaria with large drop	Malaria eliminated
Albania	1900	1950	1970
Austria	1900	1920	1950
Belarus	1900	1950	1970
Belgium	1900	1920	1950
Bosnia and Herzegovina	1900	1950	1970
Bulgaria	1900	1950	1960
Croatia	1900	1950	1970
Czech Republic	1900	1950	1960
Estonia	1900	1950	1970
Finland	1900	1920	1950
France	1900	1920	1950
Germany	1900	1920	1950
Greece	1900	1960	1970
Hungary	1900	1950	1960
Italy	1900	1950	1960
Latvia	1900	1950	1970
Lithuania	1900	1950	1970
Montenegro	1900	1950	1970
Netherlands	1900	1950	1960
Poland	1900	1930	1960
Portugal	1900	1950	1960
Republic of Moldova	1900	1950	1970
Romania	1900	1950	1970
Russian Federation	1900	1950	1970
Serbia	1900	1950	1970
Slovakia	1900	1950	1960
Slovenia	1900	1950	1970
Spain	1900	1950	1960

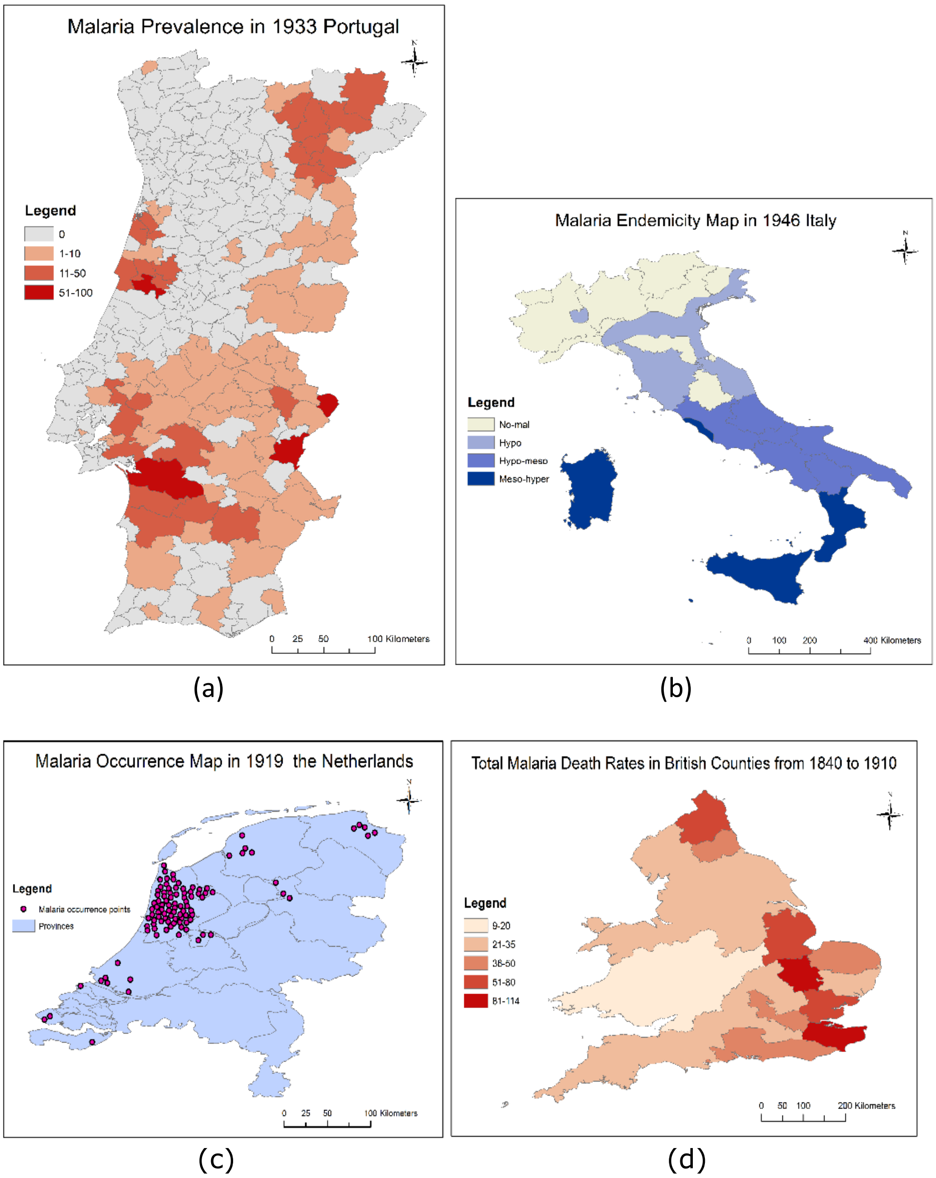
The former Yugoslav Republic of Macedonia	1900	1950	1970
Ukraine	1900	1950	1970
United Kingdom of Great Britain and Northern Ireland	1900	1920	1950

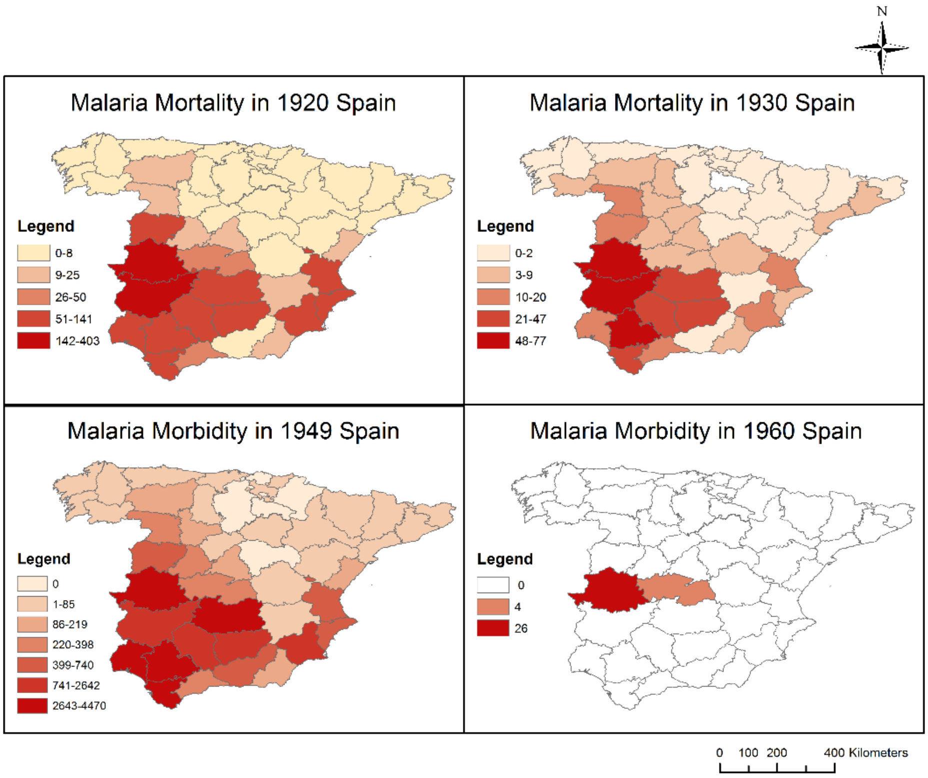
3.2.2.3 Malaria endmicity for individual countries

A systematic review of literature was undertaken to get malaria endemicity data in individual countries. In the end, malaria maps or case numbers were found in 5 countries: the Netherlands, Spain, Italy, Portugal and Britain, as updated in Figure 13.

Those malaria maps in individual countries were different in data sources, construction criteria, time and format. The map for the Netherlands was a point map according to malaria occurrence records (Swellengrebel & de Buck, 1938). Malaria maps in Spain were classified by malaria morbidity or mortality rates (Sousa et al., 2014). Malaria case and death numbers were found in the database of the Spanish Statistical Institute (Instituto Nacional de Estadistica, 2015). The four-class malaria endemicity map in Italy was stratified by pre-operational data of 1946 (Bruce-Chwatt & de Zulueta, 1980). Malaria prevalence map in 1933 Portugal was based on spleen rates (Bowden, Michailidou, & Pereira, 2008), which is an indicator of malaria prevalence (Shukla et al., 2011). In Britain, the original malaria map was made from deaths per 100,000 inhabitants in British counties from 1840 to 1910 (Kuhn et al., 2003), but here because of the crude spatial datasets, counties were dissolved by total malaria death rates.

The variations in malaria endemicity data determined that different approaches should be used to explore the associations between malaria endemicity and candidate drivers.


Malaria Prevalence in 1933 Portugal
Legend
0
1-10
11-50
51-100
0 25 50 100 Kilometers
(a)
Malaria Endemicity Map in 1946 Italy
Legend
No-mal
Hypo
Hypo-meso
Meso-hyper
0 100 200 400 Kilometers
(b)
Malaria Occurrence Map in 1919 the Netherlands
Legend
Malaria occurrence points
Provinces
0 25 50 100 Kilometers
(c)
Total Malaria Death Rates in British Counties from 1840 to 1910
Legend
9-20
21-35
36-50
51-80
81-114
0 50 100 200 Kilometers
(d)



(e)

Figure 13. Malaria maps in 5 individual European countries. (a) Malaria prevalence in 1933 Portugal, based on the level of splenic index. Figure updated from Bowden et al. (2008); (b) Malaria endemicity map in 1946 Italy. Figure updated from Bruce-Chwatt & de Zulueta (1980); (c) Malaria occurrence map in 1919 the Netherlands. Figure updated from Swellengrebel & de Buck (1938); (d) Total malaria death rates in Britain, based on the number of deaths per 100,000 inhabitants. Figure updated from Kuhn et al. (2003); (e) Malaria mortality maps in 1920 and 1930, malaria morbidity maps in 1949 and 1960. Figure updated from Sousa et al. (2014).

3.3 Data preparation

As raster datasets cannot be used directly for comparisons, it was necessary to extract and aggregate the values in raster layers first. This comprised climatic and HYDE variables. Due to the differences in original characters and the subsequent use, different approaches were undertaken to prepare those two types of datasets.

3.3.1 Climatic variables

To avoid abnormal years, climate data were all calculated for five-year averages. For example, at regional scale, the climatic variables in the years of 1900, 1946 and 1975 were actually represented by the monthly or yearly averages of 1901-1905, 1944-1948 and 1973-1977, respectively. Regional comparisons used monthly climate data to present the seasonal patterns. But at national and individual country levels, climatic variables were aggregated as yearly average values for comparisons of many countries.

Climate data were extracted using ArcGIS (ArcGIS 10.2.2, ESRI Inc, Redlands CA, USA), aggregated in Microsoft Excel, and visualized in R 2.10 (www.r-project.org). Specifically, on the platform of ArcGIS, climate data for five-year monthly or yearly averages were computed. Then raster values in different layers were extracted to points. After that, the attribute tables were exported. In Excel, climate data were divided by scaling factors, to get the true values; or further calculated for the average values of the whole country or region. Results were saved in the format of comma-separated values (csv) in order to analyse or visualize using R. The detailed steps are shown in Figure 14.

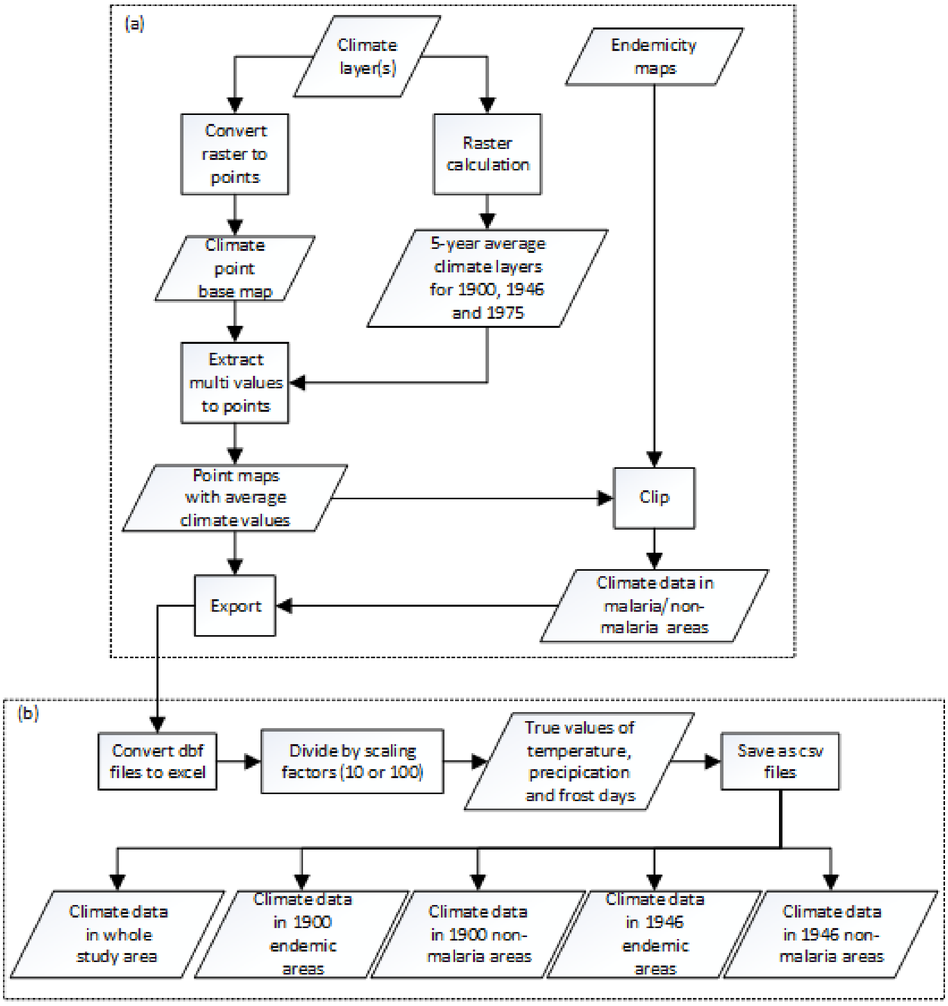


Figure 14. Flowchart of climate data preparation. Part (a) describes the procedure of data extraction in ArcGIS, and part (b) shows the process of true value calculation in Excel and resulted csv files.

3.3.2 HYDE variables

HYDE datasets comprise four spatial factors: total population, urban population, cropland and grassland. For the purpose of comparisons in space and time, four proportional variables were generated, which were the urban area percentage, the urban population percentage, the cropland percentage and the grassland percentage.

Similar to climatic variables, HYDE datasets were also extracted using ArcGIS, calculated in Excel and visualized using R. But to calculate land use and urban area percentages, the area values for each pixel were required. So that before the extraction of raster value to points, a layer containing pixel area value should be generated. In brief, a HYDE layer originally in World Geodetic System 1984 (WGS84) coordinate system, was projected to Albers Equal Area Conic coordinated system. By doing this the area value could be calculated by the function of “Calculate Geometry”. Afterwards, this layer was converted back to WGS84 coordinate system and matched with original HYDE raster layer. After the extraction and exportation of data from ArcGIS, extracted pixel values were aggregated to proportional statistics in Excel and saved as csv files. The whole workflow was displayed in Figure 15.

The process of HYDE variable preparation in 34 eliminating countries was the same to that of Europe, but the projection systems were different. As eliminating countries were located in different continents, a world HYDE layer was projected to Cylindrical Equal Area (World) coordinate system for area calculation.

Calculated areas in both European countries and eliminating ones were summed by country and compared with the true areas (http://en.wikipedia.org/wiki/List_of_countries_and_dependencies_by_area). Results showed that the calculated area values were very close to the true values.

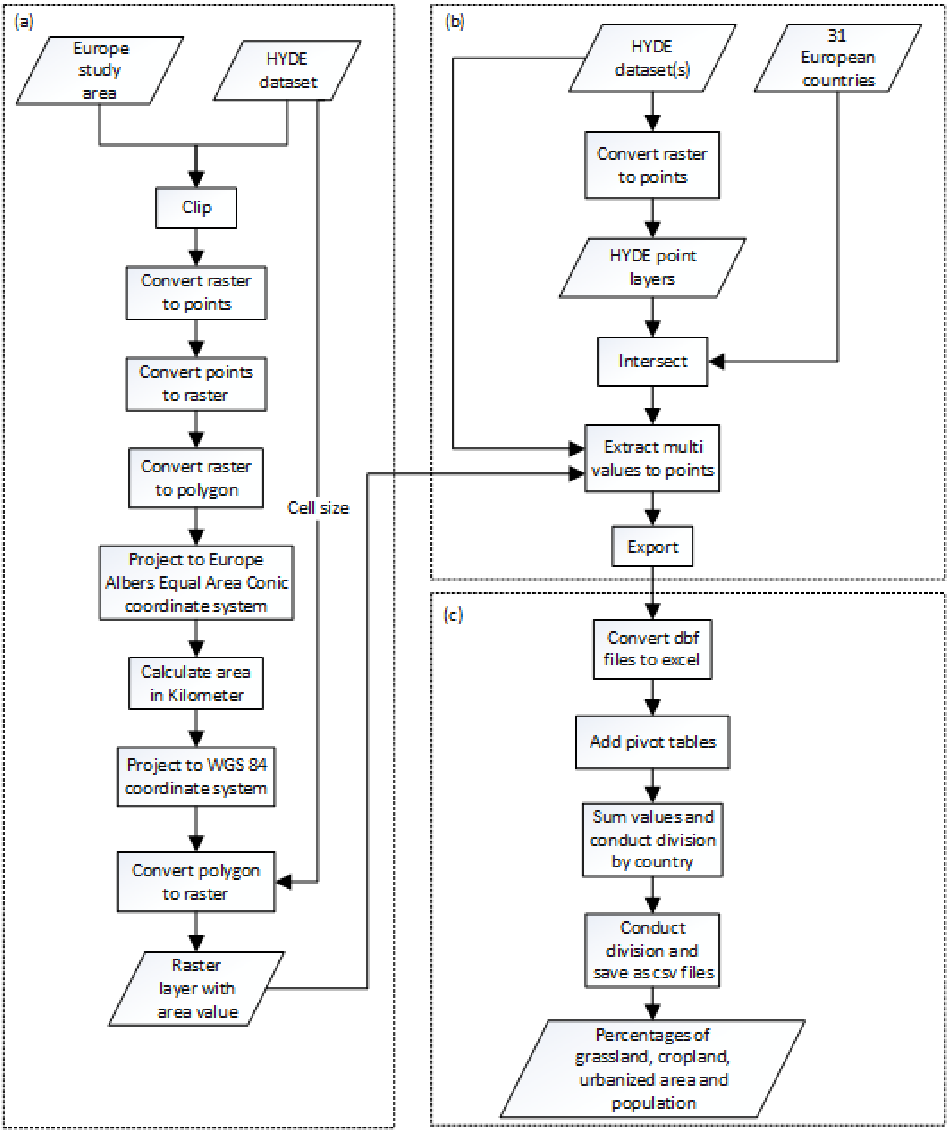


Figure 15. Flowchart of HYDE data preparation. Part (a) shows the procedure of area calculation for the cells of HYDE layers; Part (b) illustrates the process of data extraction in ArcGIS; Part (c) shows the computation from extracted raw values to percentages of urbanization and land use in Excel and resulted csv files.

3.4 Statistical tools

3.4.1 Statistical tests

To quantitatively assess the differences between or among groups, statistical tests were used. In statistical tests, two hypothesises were made in advance: the null hypothesis H_o and the alternative hypothesis H_1. H_o means that there is no difference in the true means, while *H1* expresses that the true means are significantly different (Moore et al, 2009). The level of significance is examined by p-value, which is the probability calculated assuming H_o is true. The lower the p-value, the stronger the evidence against H_o. The threshold of p-value to reject H_o is usually 0.05 (Moore et al, 2009).

There are a variety of approaches to test statistics, with different logical and computational structure, suitable for particular setting with regard to the type, distribution, number of groups. Choosing the right statistical test is crucial for the comparison (Sardanelli & Leo, 2009). In general, statistical tests are classified as parametric and non-parametric ones, determined by the distribution of the population or sample. One simple way to show the distribution of a variable in a sample is to plot a histogram (Quinn & Keough, 2002). Besides, statistical tests for comparison are also different by the number of groups (two or more than two) and the relation among groups (dependent or independent) (Sardanelli & Leo, 2009).

In this study, all tests were non-parametric. Mann-Whitney test was used for the comparisons between two paired groups; and Wilcoxon signed-rank test was used to compare two independent groups. For comparisons with more than two groups, Kruskal-Wallis test and Friedman`s test could be used for independent and repeated measures respectively (Miller, 2013; Quinn & Keough, 2002). But because of the

3.4.3 Principle component analysis

The central idea of principal component analysis (PCA) is to reduce the dimensionality of multiple interrelated variables, while remaining most information of the original datasets (Jolliffe, 2002). The new derived variables, called the principal components (PCs) are orthogonal. The variables are usually standardized to zero mean and unit variance, so that the scale difference among variables could be ignored (Quinn & Keough, 2002). The generation of new PCs is based on the calculation of covariance for each combination of variables and the diagonalization of the Covariance Matrix (Shlens, 2014). From the rotation of original variables to PCs, a loading is calculated to describe how close the variable is to PC. Due to the efficiency of variable reduction, PCA was widely used in remote sensing (Holden & LeDrew, 1998; Li & Yeh, 1998; Lu et al., 2004) and soil science (Bååth & Anderson, 2003; Facchinelli et al., 2001; Fierer et al., 2003). Besides, PCA can also be applied to detect the correlations among variables (Quinn & Keough, 2002).

In R, scaling or ordination is calculated from eigenvectors and standardized. It indicates the closeness of the variables to the PC. Scaling scores are visualized in biplots, with displaying both objects and variables in a two-dimension plane. The closer the points or the vectors are, the more relevant they are. The length of vectors represents the variance explained (Quinn & Keough, 2002).

The use of PCA here was to detect the correlations among variables at the national scale comparisons. Because of the differences in variable scales, common regression models were not able to detect those correlations.

3.4.4 Maxent

The Maxent software package is a widely used tool for species distribution modelling (SDM). It predicts the potential of species occurrence based on the presence-only data and environmental/climate layers (Phillips et al, 2006). Recently, it has become increasingly popular in epidemical studies. For example, Maxent was used to model the environment suitability for disease (Harrigan et al, 2014), predict infection prevalence under climate-change scenarios (Feria-Arroyo et al., 2014; Harrigan et al., 2014), and link vectors, environmental variables and disease outbreaks (Mughini-Gras et al., 2014). The prediction of occurrence is based on the calculation of maximum entropy. The area under the curve (AUC) of the receiver operating characteristic (ROC) is a measure of the performance of Maxent (Phillips et al., 2006). In addition, the jackknife method shows the contribution of each explanatory variable, indicating the relative importance of the variables to the prediction.

3.4.5 Regression

Multi-collinearity is a phenomenon that two or more predictor variables are highly correlated in multiple regression models. Severe collinearity can cause various problems on regression, including inclusion of irrelevant variables and unreliable parameter estimation (O'Brien, 2007), therefore a multi-collinearity test is an important step prior to regression. There are numerous ways to detect multi-collinearity (Quinn & Keough, 2002). Here in this study, two steps were taken to detect and quantify multi-collinearity (Neter, 1990): firstly, the pairwise Pearsons correlations (r) for each combination of predictor variables were computed; secondly, the variance inflation factors (VIF) was calculated. A rule of thumb to remove variables is r>0.5 and VIF>10 (Neter, 1990).

Regression models are commonly used to gauge the impact of one or a set of independent variables upon a dependent variable, thus two main purposes of regression are explanation and prediction (Mac Nally, 2000). In cases that there are many independent variables, finding the 'best fit' subset, which are most important in explaining the response variable, is essential (Quinn & Keough, 2002). Three traditional techniques to achieve the single 'best' models are forward selection, backward selection (elimination) and stepwise selection (Mac Nally, 2000; Quinn & Keough, 2002). Forward regression starts off with no explanatory variable and then adds the one with greatest correlation, followed by another, this process continues until no significant value is added or all variables have been included. Backward selection performs in the opposite way, by starting with all explanatory variables. The one with the least significant partial F statistic is dropped and the model is refitted. The process is repeated until all variables had significant partial F statistics or all variables have been tested. Stepwise selection is a combination of forward and backward selection. The commonly used threshold for F statistic is 0.05.

In the case of Spain, forward and backward regression models were used to select the most correlated variables to malaria. Before the regression models, multi-collinearity among variables was tested.

4 Results

This chapter presents the results of data analysis. The findings are showed in the following order: regional comparison, national comparison, principal component analysis at the national scale and individual country studies, as well the comparisons between European countries in three time points of malaria reduction and eliminating countries in 1900 and current time.

4.1 Regional comparisons

At the regional scale, the changes in climate, urbanization and land use were firstly presented in the whole Europe study area, then variables were compared at spatial and temporal dimensions. The baseline maps of spatial and temporal comparisons were illustrated in Figure 12, and the workflows of data preparation were explained in Figure 14 and Figure ***15***. Climate data in years of 1900, 1946 and 1975 was calculated for 5-year monthly average values (1901-1905, 1944-1948 and 1973-1977, respectively), and visualized in boxplots. To compare the statistical differences, those point data were aggregated to monthly average values, shown in tables. As HYDE layers were in decade interval, to meet with the time of 1946 and 1975, the averages of 1940 and 1950 were used for the year of 1946; and the averages of 1970 and 1980 were computed for 1975. Both urbanization and land use variables were aggregated to percentages. Results show that the spatial climate differences were much more significant than the changes as time, and all urbanization and land use variables had increased.

4.1.1 Climatic variables

Climatic variables include mean temperature, precipitation and frost day frequency. Mean temperature and precipitation were analysed monthly to show the seasonal differences; and frost day frequency was calculated yearly due to the great contrast from month to month. Due to the vast number of pixel values in climate layers, statistical tests came out with very low p-values for almost all comparisons, so instead, the monthly average values of those variables were computed to compare the differences.

4.1.1.1 Temperature

Overall trends

The changes of monthly mean temperature in 1900, 1946 and 1975 in the Europe study area are shown in Figure 16 and Table 3. Overall, temperature in Europe had increased in the first three-quarters of last century. The warming pattern was more obvious in the early stage, , with an increase of 0.39°C. From 1946 to 1975, yearly mean temperature increased by 0.17°C. Monthly, the patterns of temperature changes were not consistent. In 1946 the winter months were much colder and summer months were much hotter than the other two years. In 1975 from March to May the weather was much hotter than previous years and winter was less cold.

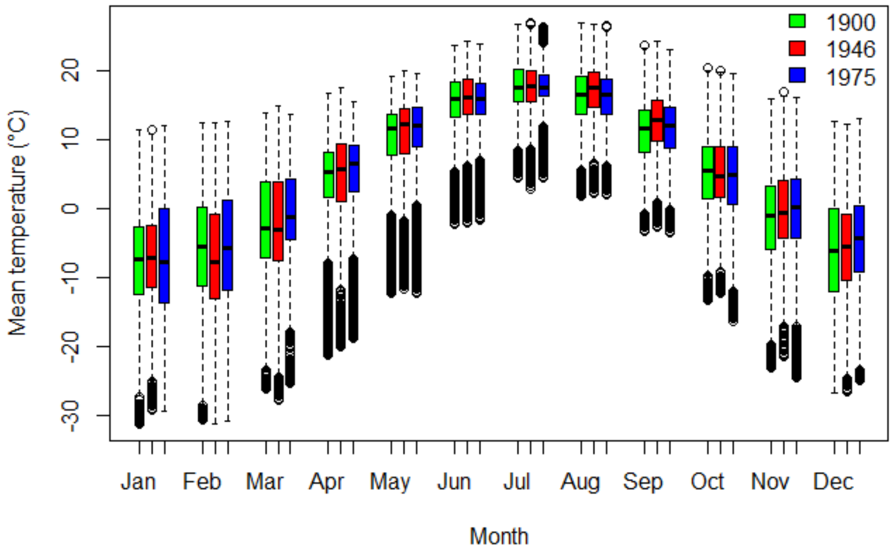


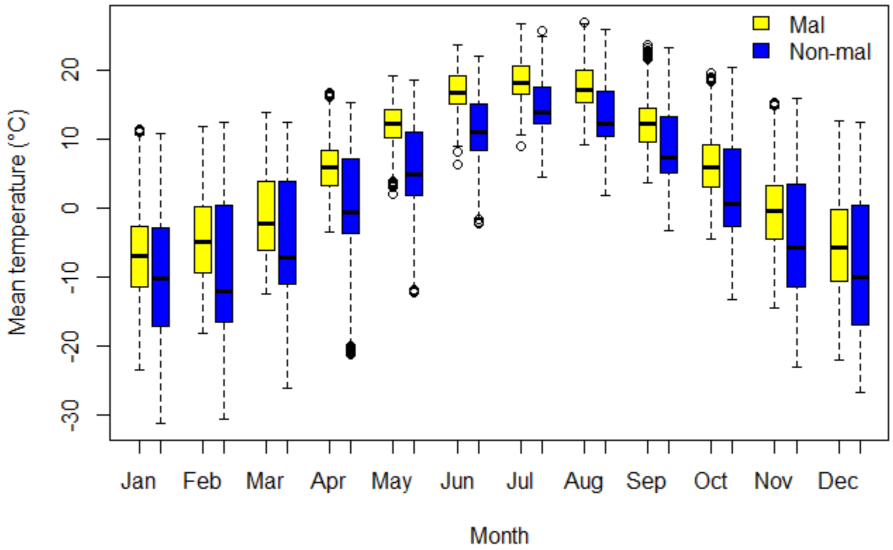
Figure 16. Boxplots showing the monthly mean temperature in 1900, 1946 and 1975 in whole study area of Europe.

Table 3. Average monthly mean temperature in 1900, 1946 and 1975 in whole study area of Europe.

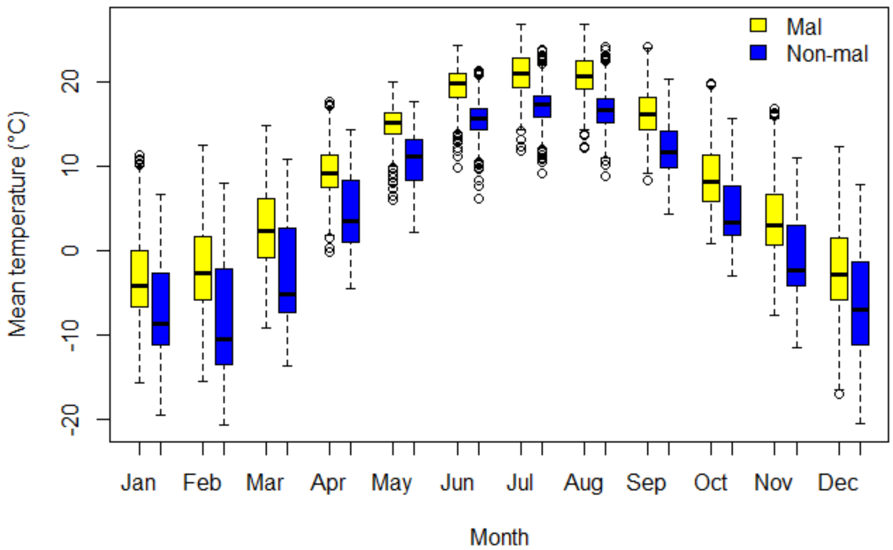
Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900	-7.55	-5.80	-2.15	4.37	10.23	15.42	17.62	16.49	11.31	5.13	-1.58	-6.23	4.77
1946	-6.79	-7.09	-2.33	4.80	10.79	15.80	17.52	17.16	12.66	5.31	-0.18	-5.70	5.16
1975	-7.33	-5.74	-0.80	5.37	11.02	15.52	17.82	16.28	11.75	4.57	-0.35	-4.21	5.33

Spatial comparisons

Spatial comparisons of temperature in malaria-free and endemic areas are displayed in Figure 17 and Table 4. It is evident that malaria-free areas had much lower temperature than endemic areas in both 1900 and 1946. In 1900, the yearly average temperature in non-malaria areas was 1.68°C, 4.23°C lower than areas with malaria transmission. Similarly, in 1946, the still endemic areas had 4.54°C higher yearly average temperature than that eliminated. Monthly, the differences in summer time were larger than winter period, but on average, endemic areas had a range of 3-6°C higher temperature than malaria-free ones.



(a)



(b)

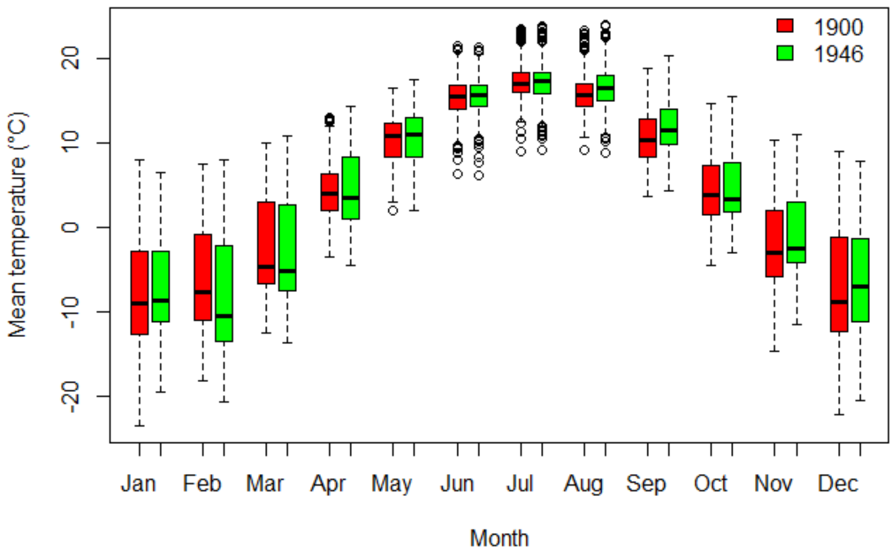
Figure 17. Boxplots showing the spatial differences in monthly mean temperature between malarious and non-malaria regions in (a) 1900; and (b) 1946.

Table 4. Average monthly temperature in malarious and non-malaria regions in 1900 and 1946.

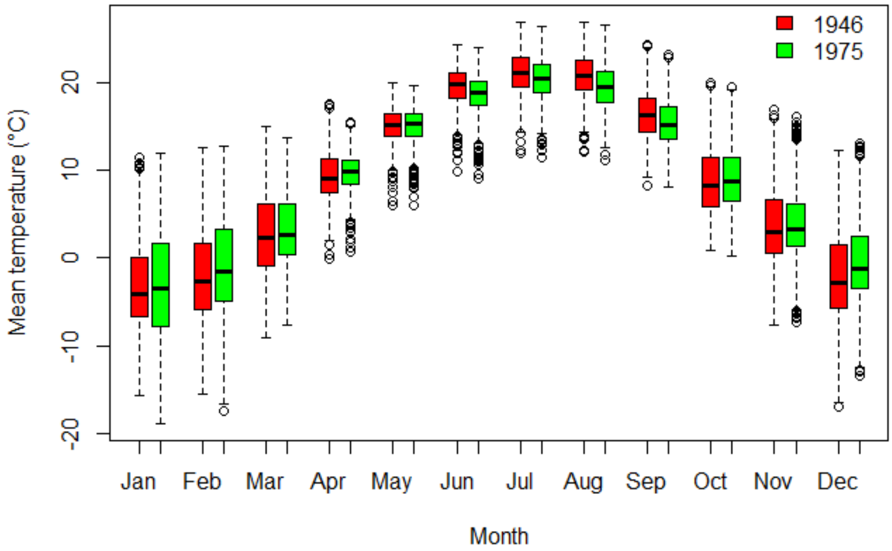
Spatial	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	-6.68	-4.60	-1.19	5.85	11.94	16.94	18.68	17.64	12.23	6.14	-0.52	-5.42	5.92
1900 Non-mal	-9.89	-9.04	-4.72	0.37	5.62	11.32	14.75	13.39	8.84	2.40	-4.46	-8.40	1.68
1946 Mal	-3.29	-2.04	2.55	9.26	14.97	19.50	21.04	20.81	16.43	8.93	3.68	-2.23	9.13
1946 Non-mal	-7.27	-8.26	-3.06	4.39	10.67	15.65	17.04	16.63	11.97	4.57	-0.87	-6.36	4.59

Temporal comparisons

The changes of mean temperature in malaria eliminated areas from 1900 to 1946 and from 1946 to 1975 are shown in Figure 18 and Table 5. In general, the changes of mean temperature by time were much less than the spatial differences. In areas that eliminated malaria between 1900 and 1946, the increase in yearly average temperature was 0.32°C. This rise was mainly contributed by warmer November and December in 1946, but was partly offset by the low temperature in February and March. For areas that achieved elimination during 1946-1975, the increase in yearly average temperature was ignorable, from 9.13°C to 9.16°C. Monthly, temperature in 1975 was generally higher in winter months and lower in summer time than three decades ago.



(a)



(b)

Figure 18. Boxplots showing the temporal changes in monthly mean temperature in malaria eliminated areas during the periods of (a) 1900-1946; and (b) 1946-1975.

Table 5. Average monthly temperature in malaria eliminated areas during 1900-1946 and during 1946-1975.

Temporal	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	-7.97	-6.43	-2.63	4.32	10.31	15.41	17.16	15.78	10.54	4.34	-2.22	-7.34	4.27
1946 Non-mal	-7.27	-8.26	-3.06	4.39	10.67	15.65	17.04	16.63	11.97	4.57	-0.87	-6.36	4.59
1946 Mal	-3.29	-2.04	2.55	9.26	14.97	19.50	21.04	20.81	16.43	8.93	3.68	-2.23	9.13
1975 Non-mal	-3.18	-1.21	3.00	9.78	15.05	18.64	20.47	19.63	15.52	9.08	3.77	-0.59	9.16

4.1.1.2 Precipitation

Overall trends

Monthly total precipitation in 1900, 1946 and 1975 in Europe are displayed in Figure 19 and Table 6. Certain seasonal patterns can be seen, but not as obvious as mean temperature. Each set of data covered a wide range of values, indicating great variations in space. Generally, precipitation was high in June, July and August, and relatively low in other months. The changes in monthly precipitation were not constant, and the magnitudes of changes were mostly within 5mm. The yearly total precipitation in Europe experienced a gentle drop from 1900 to 1946, followed by a greater increase in 1975.

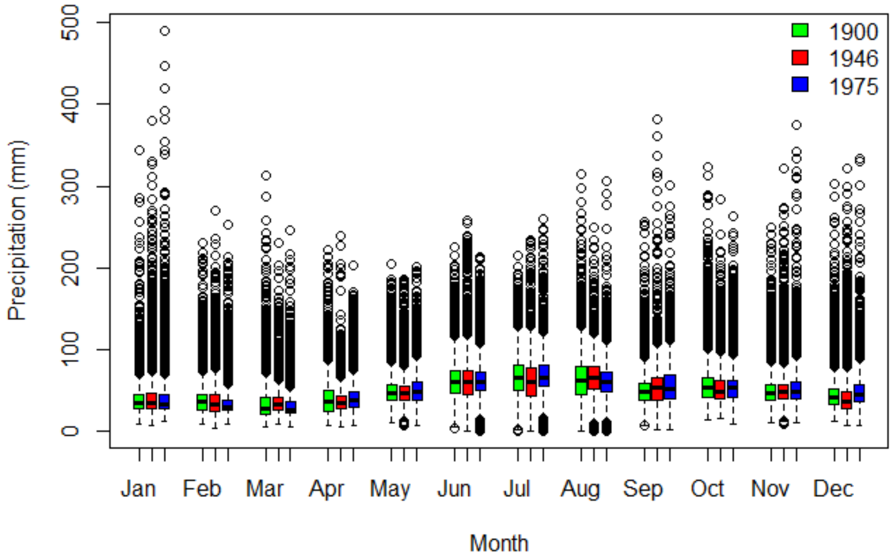


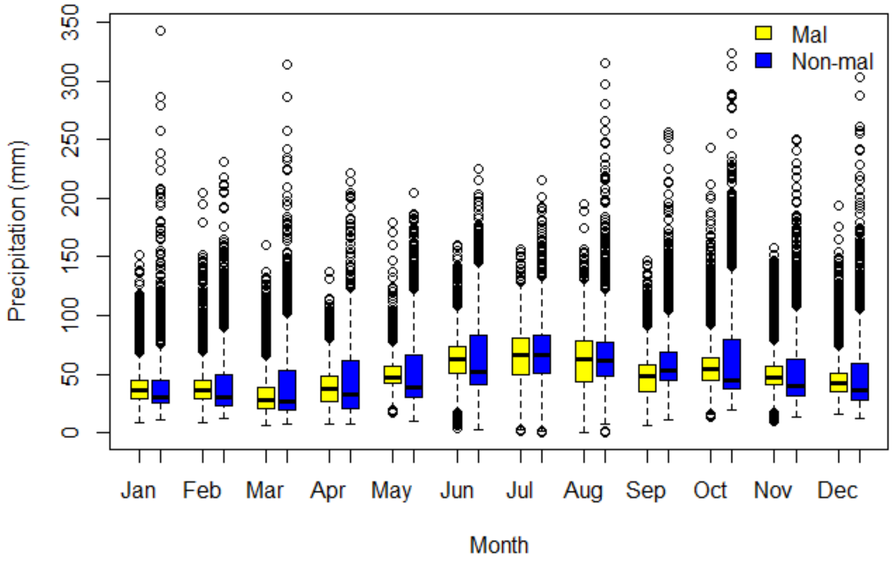
Figure 19. Monthly precipitation in 1900, 1946 and 1975 in whole study area of Europe.

Table 6. Average monthly precipitation in 1900, 1946 and 1975 in whole study area of Europe.

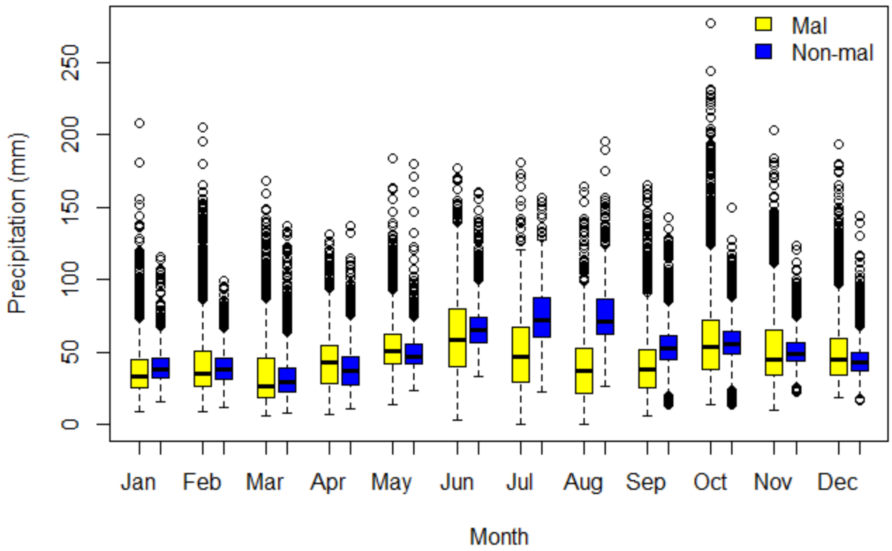
Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900	39.32	40.80	36.44	40.83	50.78	63.54	65.57	63.18	51.50	59.61	52.07	47.40	611.07
1946	42.69	39.14	36.39	38.13	49.41	62.14	60.60	64.61	54.53	54.39	52.79	44.50	599.31
1975	41.65	37.18	33.42	41.72	52.31	63.45	69.11	61.44	56.64	56.06	54.93	50.04	617.96

Spatial comparisons

Figure 20 and Table 7 present the spatial differences in precipitation in Europe malaria-free areas and endemic ones. In 1900, a consistent pattern of higher monthly precipitation in non-malaria areas than still endemic regions is seen, and this led to a remarkable difference (78.39 mm) in cumulative yearly precipitation. In 1946, monthly precipitation in areas eliminated malaria was much higher than still endemic places from June to September. But in other months, endemic areas showed slightly more precipitation. In the whole year, non-malaria areas showed a marked higher value (53.30 mm) of precipitation than endemic ones.



(a)



(b)

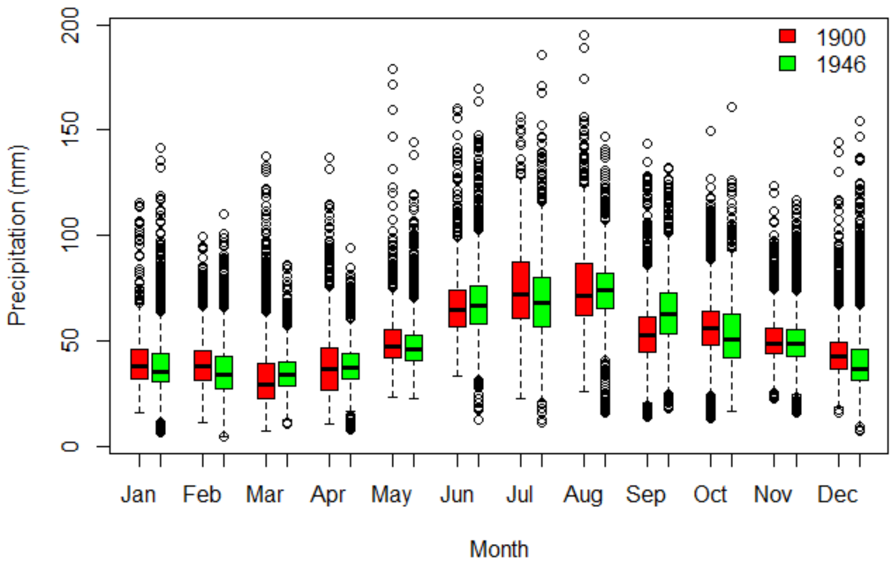
Figure 20. Boxplots showing the spatial differences in monthly precipitation between malarious and non-malaria regions in (a) 1900; and (b) 1946.

Table 7. Average monthly precipitation in malarious and non-malaria regions in 1900 and 1946.

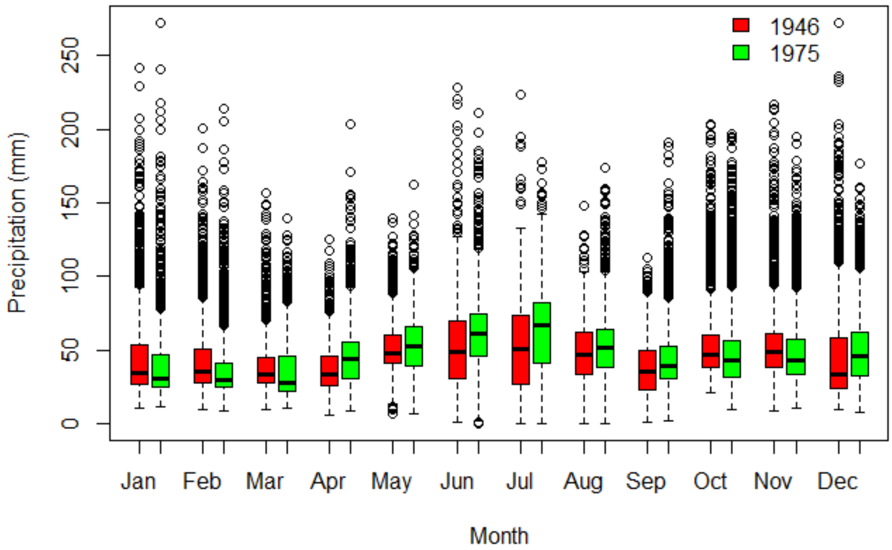
Spatial	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	38.49	39.54	33.47	39.00	49.76	62.53	64.25	61.13	47.56	56.85	51.18	46.16	589.90
1900 Non-mal	41.59	44.21	44.47	45.80	53.55	66.29	69.15	68.73	62.15	67.11	54.50	50.74	668.29
1946 Mal	45.42	43.72	39.65	37.73	51.55	52.78	50.78	47.77	37.99	54.96	54.89	47.23	564.46
1946 Non-mal	39.45	36.99	34.85	38.80	48.33	67.98	68.82	74.50	62.89	52.55	50.77	41.82	617.76

Temporal comparisons

Monthly total precipitation data in areas eliminated malaria from 1900 to 1946 and from 1946 to 1975 are displayed in Figure 21 and aggregated in Table 8. From 1900 to 1946, with slight ups and downs in monthly precipitation, the cumulative yearly precipitation had a small decline (5.79 mm). During the later time, due to the great increases in precipitation in June and July and relatively small variations in the rest of months, non-malaria areas had approximately 30 mm higher precipitation than endemic regions.



(a)



(b)

Figure 21. Boxplots showing the temporal changes in monthly precipitation in malaria eliminated areas during the periods of (a) 1900-1946; and (b) 1946-1975.

Table 8. Average monthly precipitation in malaria eliminated areas during 1900-1946 and 1946-1975.

Temporal	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	39.86	39.26	34.31	38.79	49.49	66.09	74.41	74.96	53.86	57.18	50.96	44.38	623.55
1946 Non-mal	39.45	36.99	34.85	38.80	48.33	67.98	68.82	74.50	62.89	52.55	50.77	41.82	617.76
1946 Mal	45.42	43.72	39.65	37.73	51.55	52.78	50.78	47.77	37.99	54.96	54.89	47.23	564.46
1975 Non-mal	40.25	39.11	36.53	45.73	54.37	62.75	63.44	51.76	46.10	50.62	51.08	52.33	594.08

4.1.1.3 Frost day frequency

Overall trends

The overall trends of frost day frequency in Europe were similar to that of temperature, but opposite in values. Data of yearly frost days are displayed in Figure 22, and monthly average frost days are presented in Table 9. Because of the high temperature in June, July and August, Europe had the least frost days in those months. The yearly changes of frost days were 9 days decrease from 1900 to 1946 followed by 3 days increase in 1975.

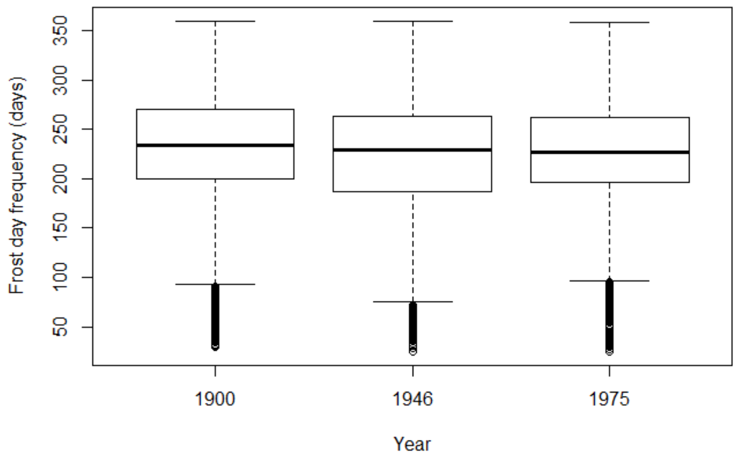


Figure 22. Yearly frost day frequency in 1900, 1946 and 1975 in whole study area of Europe.

Table 9. Average monthly frost day frequency in 1900, 1946 and 1975 in whole study area of Europe.

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900	30.37	27.52	29.12	23.69	15.67	5.89	3.98	2.70	11.81	22.84	27.87	29.99	231.44
1946	30.34	27.67	28.92	22.87	14.72	5.00	4.30	2.14	9.10	23.18	24.28	30.01	222.52
1975	30.09	27.32	29.10	23.07	14.13	5.07	3.21	2.48	10.73	22.78	27.47	29.79	225.25

Spatial comparisons

Spatially, the differences in frost day frequency between malaria-free areas and endemic regions are shown in Figure 23 and Table 10. In general, non-malaria areas had significantly higher frost day frequency than still endemic ones in both years. This difference mainly occurred in warm months.

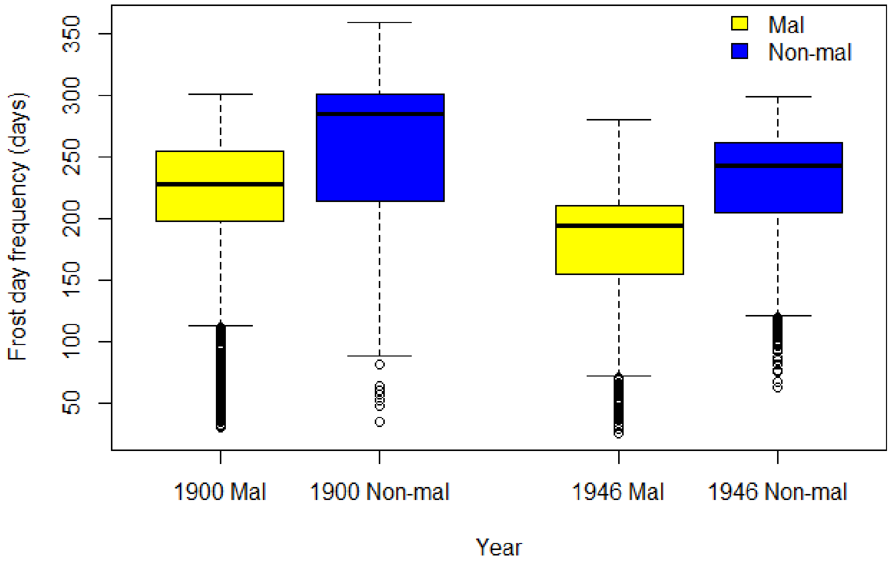


Figure 23. Boxplots showing the spatial differences in yearly frost day frequency between malarious and non-malaria areas in 1900 and 1946.

Table 10. Average monthly frost day frequency in malarious and non-malaria regions in 1900 and 1946.

Spatial	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	30.25	27.42	28.90	23.04	13.55	3.57	2.67	1.39	10.39	22.23	27.65	29.82	220.89
1900 Non-mal	30.70	27.80	29.73	25.46	21.39	12.14	7.51	6.24	15.63	24.50	28.44	30.42	259.97
1946 Mal	29.46	26.80	27.18	17.63	6.14	1.29	1.88	0.69	4.93	16.82	18.90	28.87	180.59
1946 Non-mal	30.69	27.99	29.45	24.67	16.38	3.89	3.56	1.19	9.01	25.66	26.35	30.45	229.30

Temporal comparisons

Temporal comparisons of frost day frequency in Europe are presented in Figure 24 and Table 11. In total, the temporal differences were much smaller than that at the spatial dimension. Similar to whole area comparisons, from 1900 to 1946, frost day frequency decreased by 8 days; and from 1946 to 1975, a small increase of 6 days in frost days was shown.

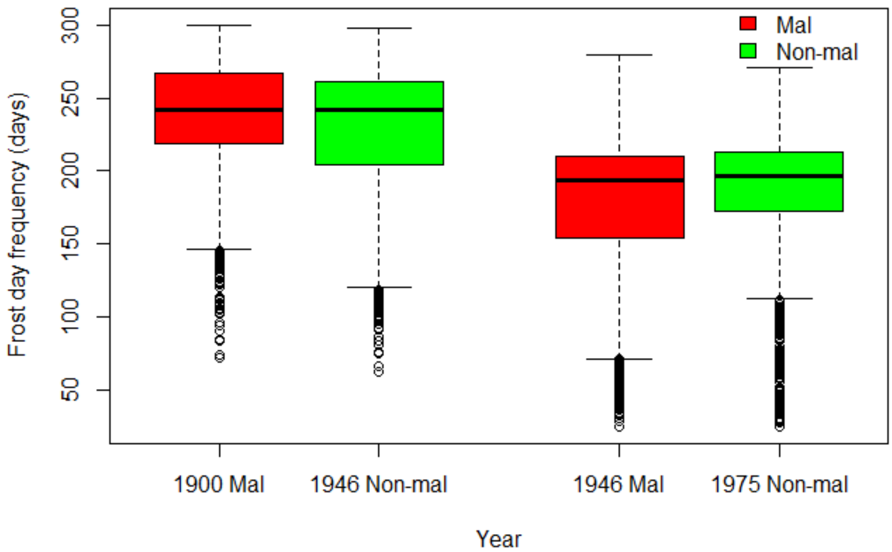


Figure 24. Boxplots showing the temporal changes in yearly total frost day frequency in malaria eliminated areas during the periods of (a) 1900-1946; and (b) 1946-1975.

Table 11. Average monthly precipitation in malaria eliminated areas during 1900-1946 and 1946-1975.

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Yearly
1900 Mal	30.77	27.93	29.64	25.42	17.23	4.76	3.40	1.91	12.13	25.38	28.54	30.46	237.56
1946 Non-mal	30.69	27.99	29.45	24.67	16.38	3.89	3.56	1.19	9.01	25.66	26.35	30.45	229.30
1946 Mal	29.46	26.80	27.18	17.63	6.14	1.29	1.88	0.69	4.93	16.82	18.90	28.87	180.59
1975 Non-mal	29.15	26.28	27.53	16.73	5.54	1.57	1.70	1.08	6.21	16.38	25.60	28.70	186.47

4.1.2 Urbanization

The percentages of urban area and urban population were compared in 1900, 1946 and 1975 in whole Europe study area, and at spatial and temporal scales based on Figure 12.

Overall trends

In total, significant increases of urbanization – both urbanized area and population – were seen during the period of 1900 to 1975 in Europe, as shown in Figure 25. The increases in the proportion of urban area were from 3.19% in 1900 to 5.63% in 1946, and reached 13.22% in 1975. The percentages of urban population had greatly increased as well. In 1975, 64.71% population were living in cities, about twice as much as that in 1900.

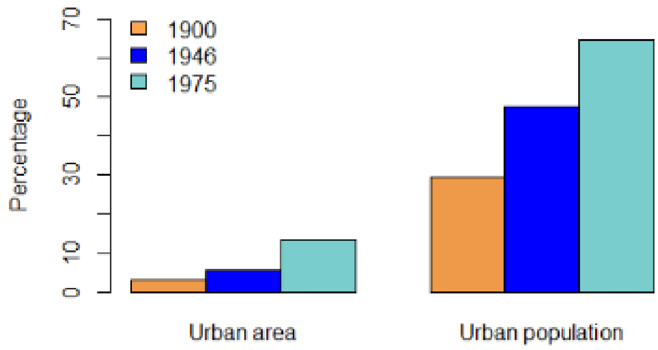
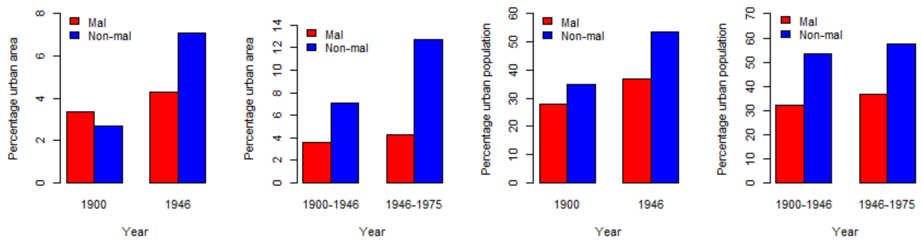


Figure 25. Bar plots showing the increases of the percentage urban area and the percentage urban population in 1900, 1946 and 1975 in whole study area of Europe.

Spatial and temporal comparisons

Figure 26 presents the spatial and temporal comparisons in the percentages of urban area and population. Spatially, in 1900, endemic areas had slightly higher rate of urban area than malaria-free areas. But in 1946, malaria eliminated areas had much higher proportion of land urbanized. For the percentage of urban population, malaria-free areas had higher rates than those still malarious. Temporally, both urban area and population had significantly expanded, showing the same trends as the overall comparisons.



(a) (b) (c) (d)

Figure 26. Spatial and temporal comparison of the percentage urban area and the percentage urban population. (a) shows the differences in the percentage urban area between malarious and non-malaria areas in 1900 and 1946; (b) shows the changes in the percentage urban area in areas eliminated malaria during 1900-1946 and 1946-1975; (c) shows the differences in the percentage urban population between malarious and non-malaria areas in 1900 and 1946; (d)

shows the changes in the percentage urban population in areas eliminated malaria during 1900-1946 and 1946-1975.

4.2.3 Land use

Same as urbanization, the percentages of cropland and grassland were compared in 1900, 1946 and 1975 in whole Europe study area, as well as at spatial and temporal scales based on Figure 12.

Overall trends

Both cropland and grassland underwent certain increases in whole Europe study area, as shown in Figure 27.

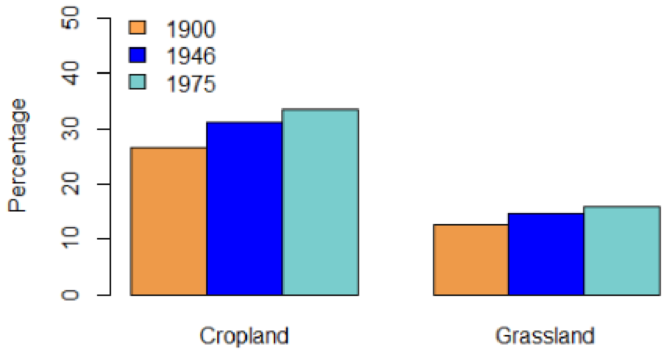
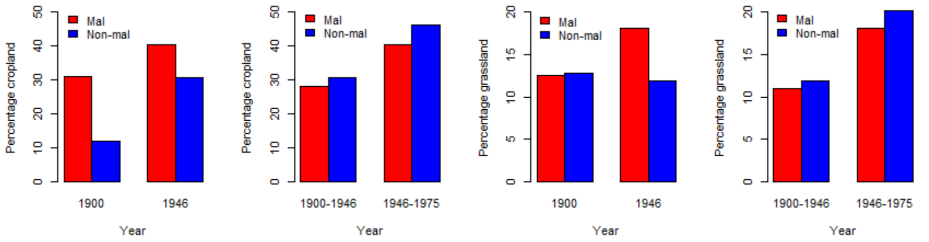


Figure 27. Bar plots showing the increases of the percentage cropland and the percentage grassland in 1900, 1946 and 1975 in whole study area of Europe.

Spatial and temporal comparisons

Spatial and temporal comparisons of cropland and grassland percentages are shown in Figure 28. Spatially, areas with malaria transmission had higher percentages of cropland than eliminated regions. The grassland percentage in 1900 was almost the same in endemic or eliminated areas, but in 1946, endemic area had higher proportion of grassland. Temporally, both cropland and grassland had certain growths during the time of malaria elimination, showing the same trends as the whole Europe comparisons.



(a) (b) (c) (d)

Figure 28. Spatial and temporal comparisons of the percentage cropland and the percentage grassland. (a) shows the differences of the percentage cropland in malarious and non-malaria areas in 1900 and 1946; (b) shows the changes of the percentage cropland in areas eliminated malaria from 1900 to 1946 and that from 1946 to 1975; (c) shows the differences of the percentage grassland in malarious and non-malaria areas in 1900 and 1946; (d) shows the changes of the percentage grassland in areas eliminated malaria from 1900 to 1946 and that from 1946 to 1975.

4.2 National comparisons

This section is composed of two main parts: individual variable comparisons at the time of 1900, malaria with large drop and malaria eliminated; and analysis of all variables by PCA, at each of the three time points.

4.2.1 Individual variable comparisons

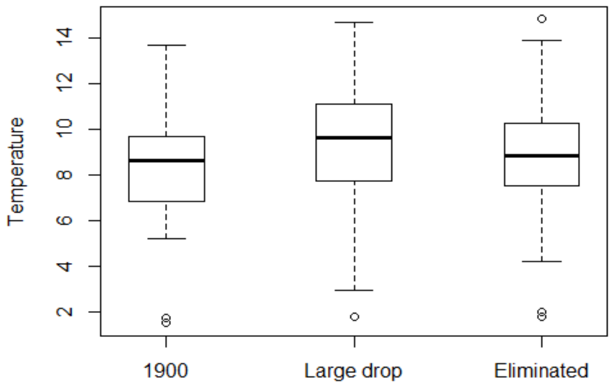
Nine individual variables, including climatic variables (temperature, precipitation and frost day frequency), GDP per capita, life expectancy, urbanization (urban area and urban population), land use change (cropland and grassland percentages). Each of those variables was compared at the time of 1900, malaria with large drop and malaria eliminated.

4.2.1.1 Climate change

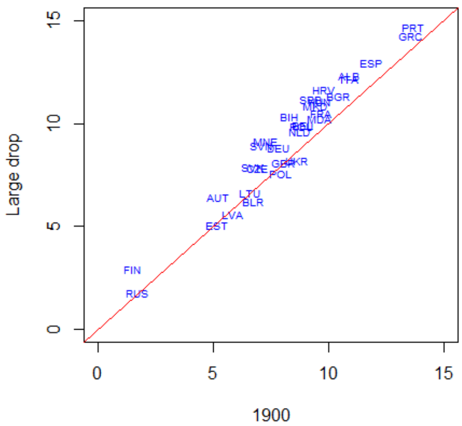
Yearly mean temperature, precipitation and frost day frequency were calculated by country to see the climate changes along with the reduction of malaria in last century.

Temperature

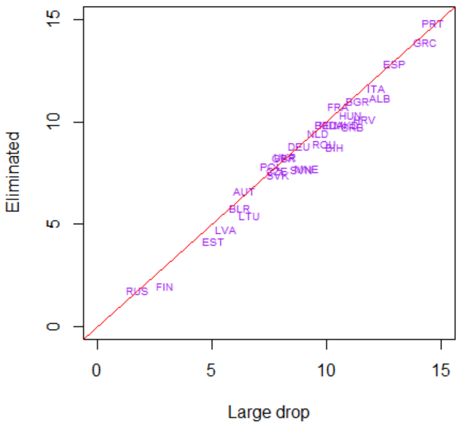
As can be seen in Figure 29, the changes in yearly temperature by country were not consistent at the time of 1900, malaria with large drop and malaria eliminated. During the first time interval, most countries underwent more or less increases in temperature. But in the later period, most countries had decreased temperature from malaria with large drop to elimination.



(a)



(b)



(c)

Figure 29. Plots showing the changes in temperature across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of temperature for three time points comparison; (b) Scatterplot showing the changes in temperature from 1900 to malaria with large drop; (c) Scatterplot showing the changes in temperature from the year of malaria with large drop to that malaria was eliminated. The ISO country abbreviation for country name is used on the scatterplots (http://www.iso.org/iso/english_country_names_and_code_elements) and the one-to-one lines were visualized. Country codes above the one-to-one lines indicate the increase of values, and vice versa.

Precipitation
The changes of precipitation had more fluctuations than temperature, as shown in Figure 30. Precipitation at the time of malaria with large drop showed no much difference from 1900 (Wilcoxon test: z=1.705, p-value=0.09). During the period of final elimination, precipitation in Europe had significantly increased (Wilcoxon test: z=-3.253, p-value<0.001).

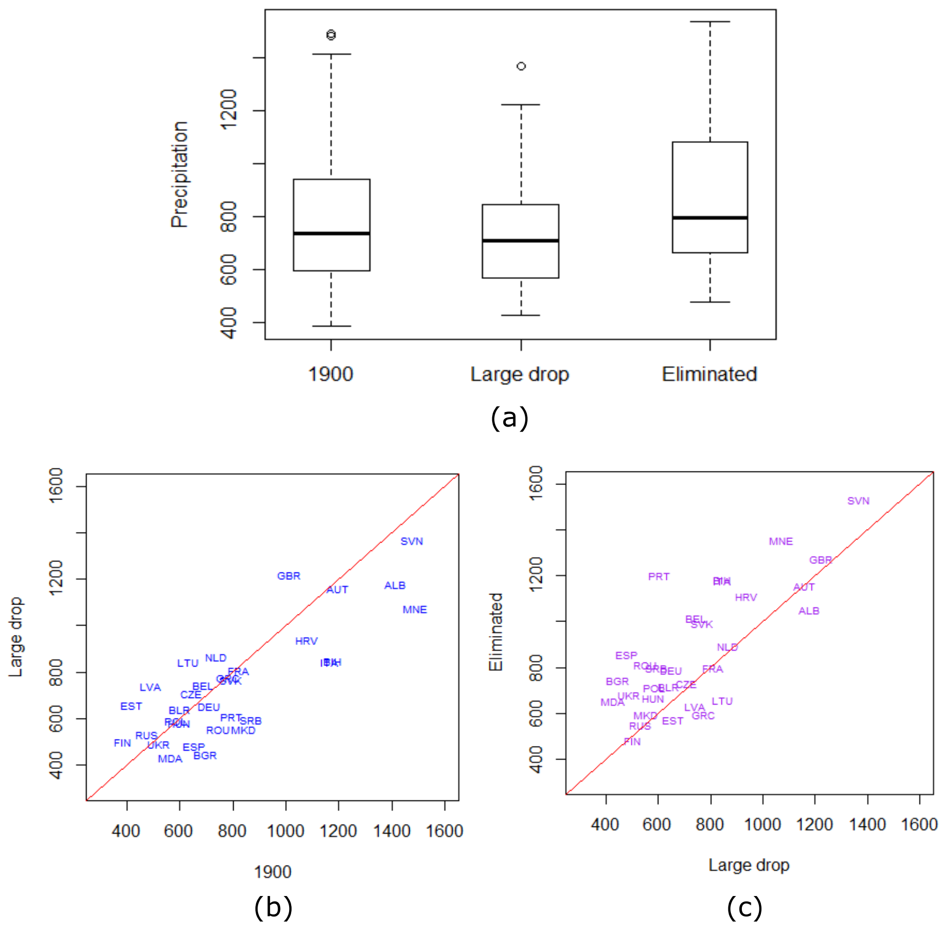


Figure 30. Plots showing the changes in precipitation across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of precipitation for three time points comparison; (b) Scatterplot showing the changes in precipitation changes from 1900 to malaria with large drop; (c) Scatterplot showing the changes in precipitation from the year of malaria with large drop to that malaria was eliminated.

Frost day frequency

Figure 31 displays the changes of frost day frequency in European countries across the years of 1900, malaria with large drop and malaria eliminated. The trend was similar to that of temperature, as the colder the temperature, the more the frost days, and vice versa. During the period of large drop of malaria, the decreases in frost day frequency were seen (Wilcoxon test: z=4.292, p-value<0.0001). From low transmission to elimination of malaria, frost day frequency was increased (Wilcoxon test: z=-2.214, p-value<0.05).

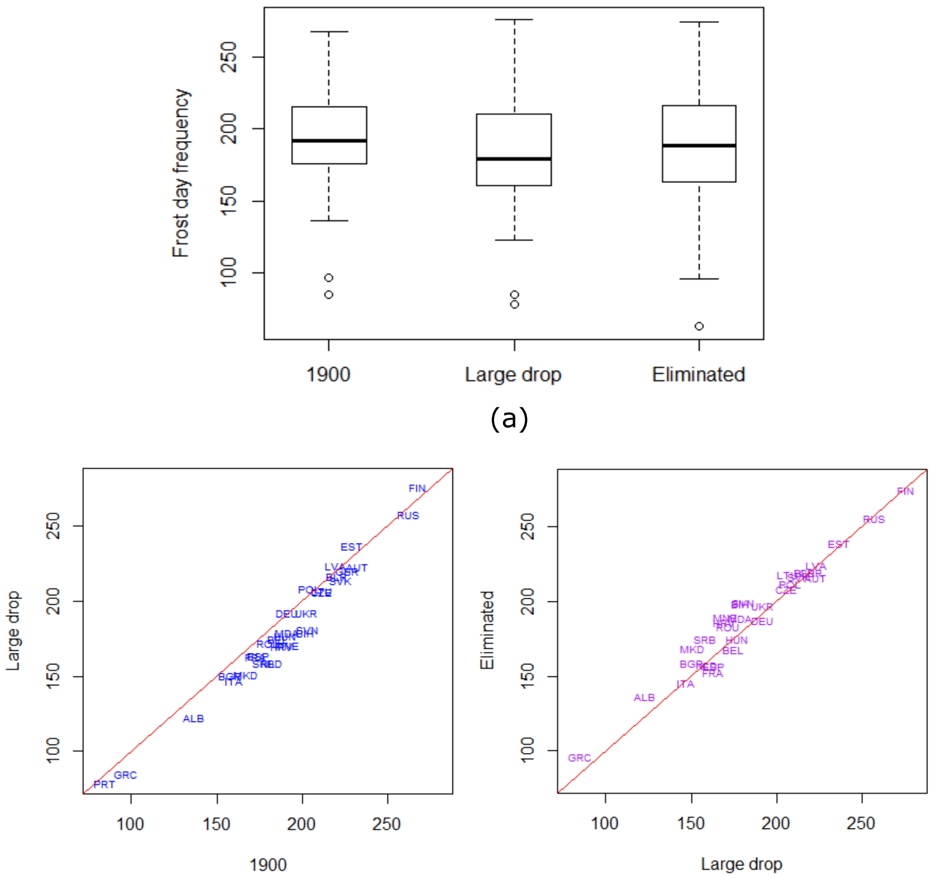
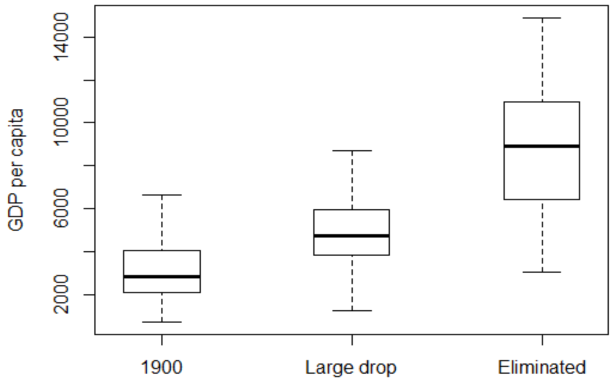


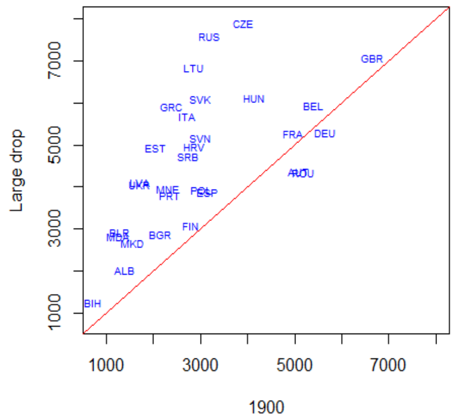
Figure 31 Plots showing the changes in frost day frequency across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of yearly frost day frequency for three time points comparison; (b) Scatterplot showing the changes in frost day frequency changes from 1900 to malaria with large drop; (c) Scatterplot showing the changes in frost day frequency from the year of malaria with large drop to that malaria was eliminated.

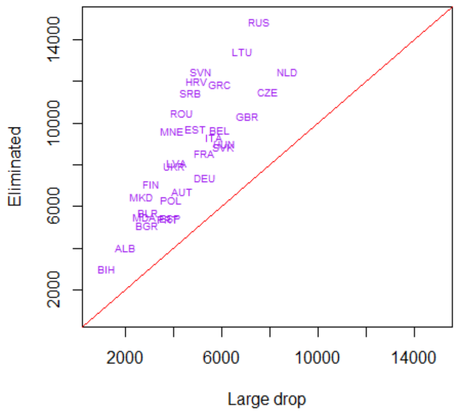
4.2.1.2 GDP per capita

The changes of GDP per capita in European countries are presented in Figure 32. Apparently, the incomes in those countries had been increasing along with the reduction of malaria. From 1900 to the year malaria with large drop, only Germany, Austria and Romania showed small decreases in GDP. But those three countries were all among upper or middle-income countries in Europe. The rest of countries had different amounts of GDP growth. From the large of malaria to final elimination, GDP was significantly increased in all countries.



(a)





(b) (c)

Figure 32. Plots showing the changes in GDP per capita across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of GDP per capita for three time points comparison; (b) Scatterplot showing the changes in GDP per capita from 1900 to malaria with large drop; (c) Scatterplot showing the changes in GDP per capita from malaria with large drop to malaria elimination.

4.2.1.3 Life expectancy

The continuous increases of life expectancy in Europe across the three time points are displayed by Figure 33. The major changes occurred during the period of 1900 to the large decline of malaria. At the time that malaria was eliminated, all countries arrived to the similar level of life expectancy.

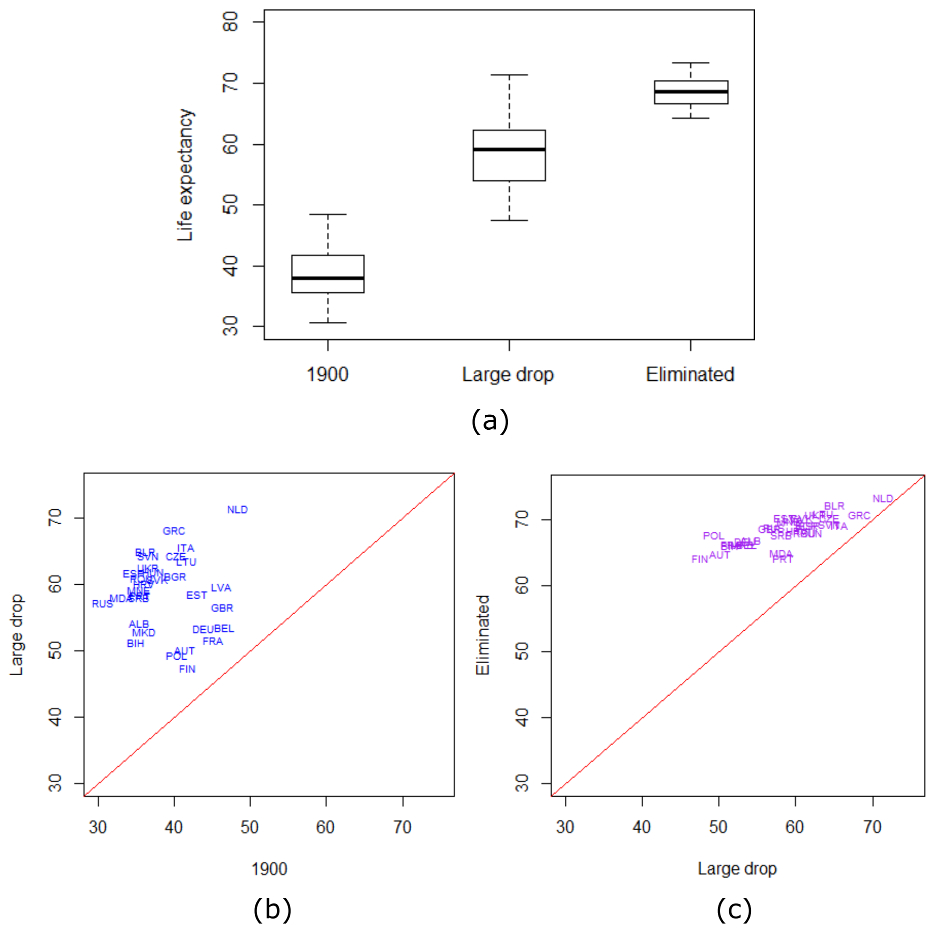


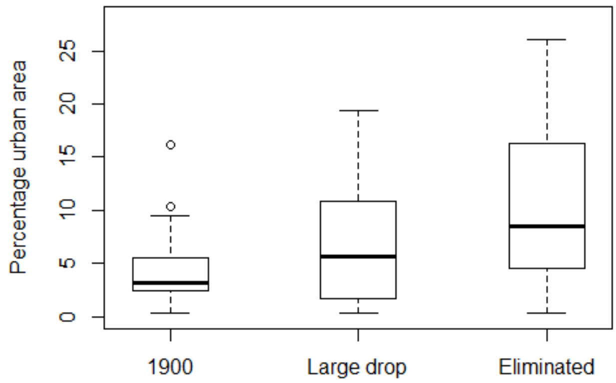
Figure 33. Plots showing the changes in life expectancy across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of life expectancy three time points comparison; (b) Scatterplot showing the changes in life expectancy changes from 1900 to malaria with large drop; (c) Scatterplot showing the changes in life expectancy changes from the year of malaria with large drop to that malaria was eliminated.

4.2.1.4 Urbanization

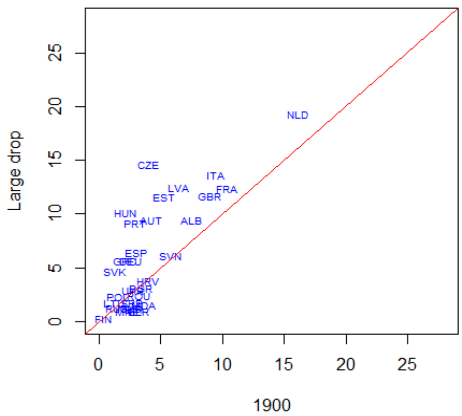
Significant increases in the percentages of urbanized area and population were seen in Europe along with the reduction of malaria in last century.

Urban area

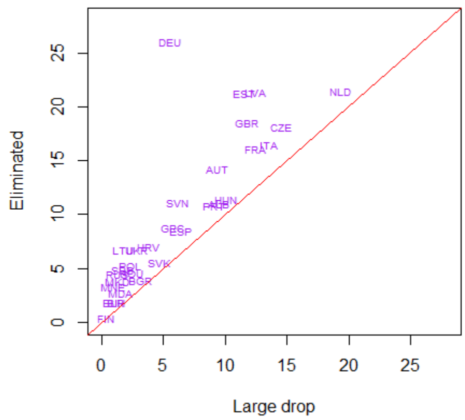
The changes in the percentage of urban area in Europe are shown in Figure 34. Overall, urban area had increased during both time periods. From 1900 to malaria with large drop, about half of studied countries had increased urban land. Countries with either no change or showing decreased urban area had low rates of urbanized area in 1900. In total, the proportions of urban area had increased (Wilcoxon test: z=-2.91, p-value<0.05). From low transmission to elimination, all countries had more land urbanized, although the increases in countries originally with low percentages of urbanized land were generally smaller.



(a)



(b)



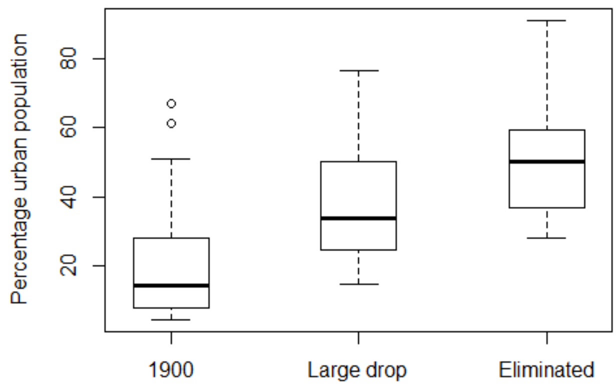
(c)

Figure 34. Plots showing the changes in the percentage urban area across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of the percentage urban area for three time points comparison; (b) Scatterplot showing the changes in the percentage urban area from 1900 to malaria with large drop; (c) Scatterplot showing the changes in the percentage urban area from the year of malaria with large drop to that malaria was eliminated. As Belgium had extremely high value of urbanized area (30.47%, 42.10% and 68.09%, respectively), to reveal the general trend in Europe, the values of urban area in Belgium was not visualized in the graphs.

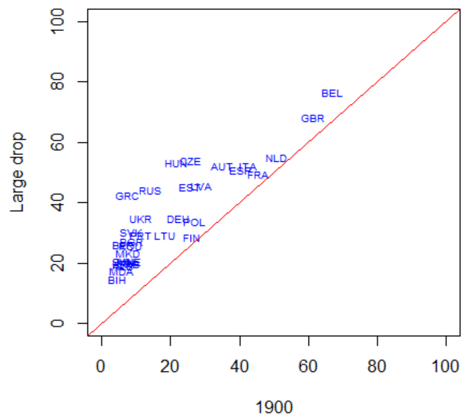
Urban population

As shown in

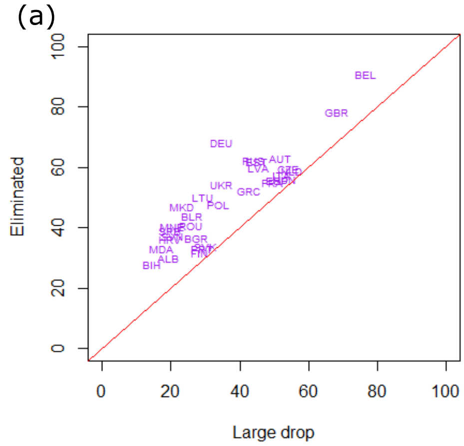
Figure ***35***, during both periods of malaria reduction, the increases in the proportion of urban population were significant.



(a)



(b)



(c)

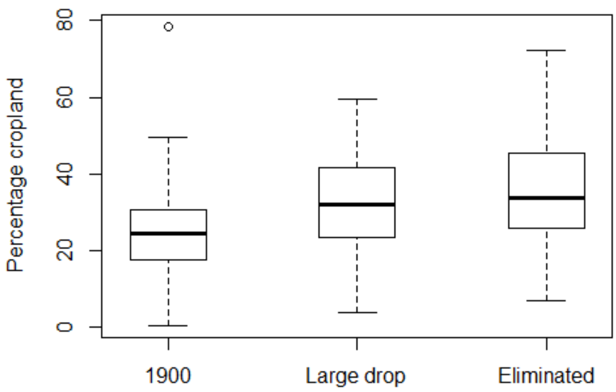
Figure 35. Plots showing the changes in the percentage urban population across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of the percentage urban population for three time points comparison; (b) Scatterplot showing the changes in the percentage urban population from 1900 to malaria with large drop; (c) Scatterplot showing the changes in the percentage urban population from the year of malaria with large drop to that malaria was eliminated.

4.2.1.5 Land use change

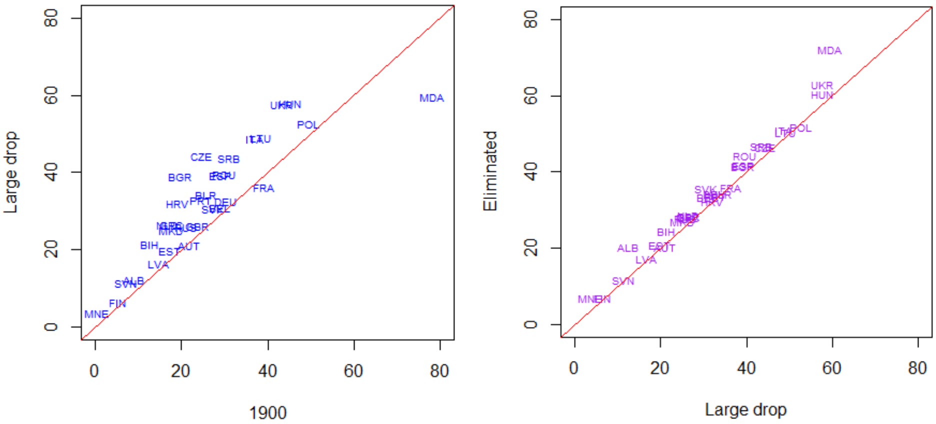
The increases in the percentages of cropland and grassland mainly occurred during the period of large drop of malaria.

Cropland

The main increases of the cropland percentage were from 1900 to malaria with large drop, as can be seen in Figure ***36***. The only country that experienced significant decrease of cropland during this period was Moldova, which had the highest cropland percentage among the 31 countries. Differently, from low endemicity of malaria to elimination, there was not much change in cropland cultivation except some small increases.



(a)

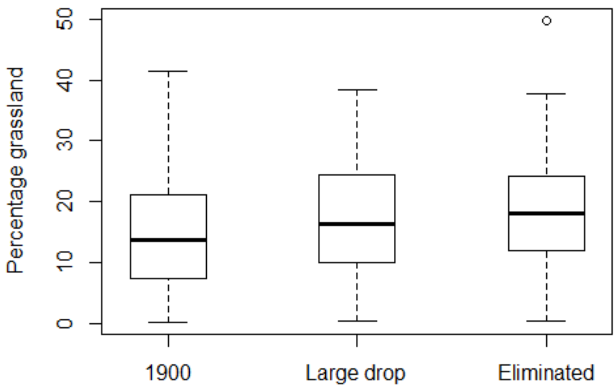


(b) (c)

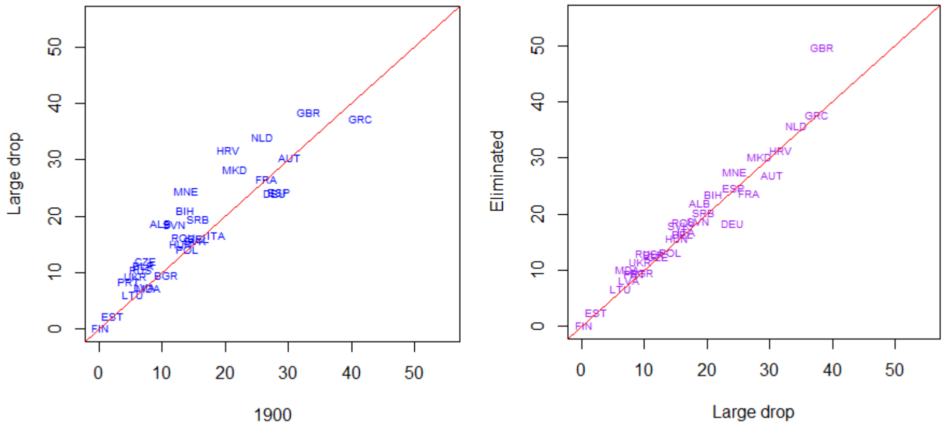
Figure 36. Plots showing the changes in the percentage cropland across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of the percentage cropland for three time points comparison; (b) Scatterplot showing the changes in the percentage cropland from 1900 to malaria with large drop; (c) Scatterplot showing the changes in the percentage cropland from the year of malaria with large drop to that malaria was eliminated.

Grassland

Similar to cropland, the main changes in the grassland percentage were in the early stage of malaria reduction, as shown in Figure ***37***. Roughly half of the countries had more proportions of grassland at the time of malaria with large drop than 1900, with the others remaining the same or slightly decreasing. From the large drop of malaria to elimination, apart from the significant increase in UK and moderate decreases in Germany, Austria and France, grassland in other countries did not show much changes.



(a)



(b) (c)

Figure 37. Plots showing the changes in the percentage grassland across the years of 1900, malaria with large drop and malaria eliminated: (a) Boxplot of the percentage grassland for three time points comparison; (b) Scatterplot showing the changes in the percentage grassland from 1900 to malaria with large drop; (c) Scatterplot showing the changes in the percentage grassland from the year of malaria with large drop to that malaria was eliminated.

4.2.2 All variable analysis

The main purpose of using standardized PCA in this study is to find the correlations among variables. As frost day frequency is highly correlated with temperature, the variable of frost day frequency was omitted from the PCA. Variables used for PCA are presented in Table 12, as well as their abbreviations displayed in biplots.

Table 12. Variables for PCA and their corresponding abbreviations.

Variables	Abbreviations
Mean temperature	tem
Yearly precipitation	pre
GDP per capita	GDP
Life expectancy	life_ex
Urban area percentage	ur_area
Urban population percentage	ur_pop
Cropland percentage	crop
Grassland percentage	grass

PCA was carried out for those three time points of 1900, malaria with large drop and malaria eliminated, respectively. The first three or four

PCs were highlighted as they explained over 70% of the total variance, and they were displayed by biplot as well.

4.2.2.1 1900

In 1900, the variances of PCs are shown in Figure 38. As can be seen, first three PCs represent the most of the original datasets. The importance of those three components is presented in Table 13. It shows that the proportions of PC1, PC2 and PC3 are 0.3815, 0.2078 and 0.1661, taking up 0.7554 in total.

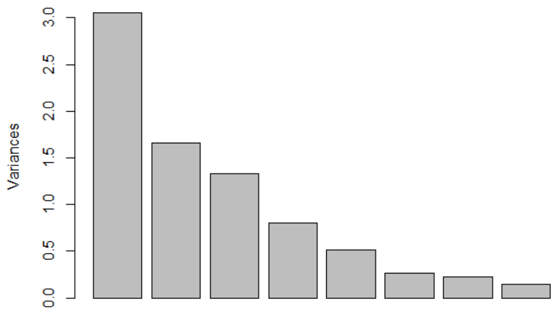
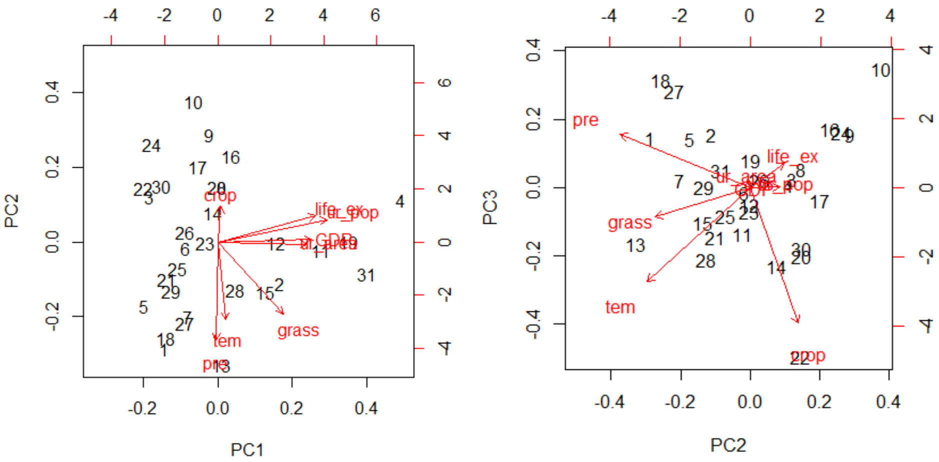


Figure 38. Screeplot of PCA in 1900.

Table 13. Importance of PC1, PC2, and PC3 in 1900 PCA.

	PC1	PC2	PC3
Standard deviation	1.747	1.2893	1.1529
Proportion of Variance	0.3815	0.2078	0.1661
Cumulative Proportion	0.3815	0.5893	0.7554

Two biplots illustrating PC1 and PC2, PC2 and PC3 are shown in Figure 39. The variables of GDP, life expectancy, percentages of urban area and population are mainly represented by PC1. The closeness of those four variables indicate the high correlations of them. Besides, land use and climatic variables are mostly shown in PC2 and PC3, but there is no consistent correlation seen.



(a) (b)

Figure 39. Biplots of (a) PC1 and PC2; (b) PC2 and PC3 of PCA in 1900.

4.2.2.2 Malaria with large drop

The importance of each PC for the time point of malaria with large drop is shown in Figure 40 and Table 14. The first three PCs carry the major information of the whole datasets, which are 0.3125, 0.2235 and 0.1876, respectively, and in total 0.7237.

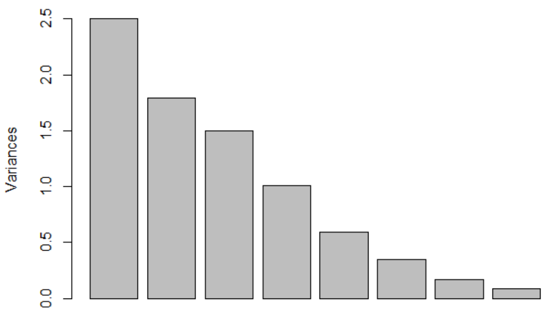
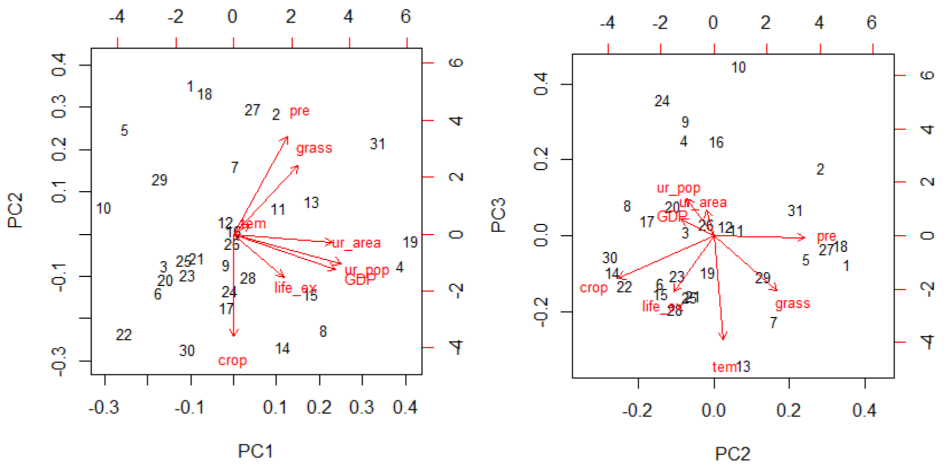


Figure 40. Screeplot of PCA at the time of malaria with large drop.

Table 14. Importance of components for the time malaria with large drop.

	PC1	PC2	PC3
Standard deviation	1.5813	1.3373	1.2251
Proportion of Variance	0.3125	0.2235	0.1876
Cumulative Proportion	0.3125	0.5361	0.7237

The first three PCs are displayed by two biplots in Figure 41. Similar to 1900, the variables of GDP, life expectancy and urbanization show high associations in PC1. But to a smaller proportion in PC3, life expectancy is against GDP and urbanization, which suggests that life expectancy increased faster than economic development and urbanization. Variables of cropland and grassland are still in the same plane as temperature and precipitation, as shown in PC2 and PC3.



(a) (b)

Figure 41. Biplots of (a) PC1 and PC2; (b) PC2 and PC3 at the time of malaria with large drop.

4.2.2.3 Malaria eliminated

The screeplot and importance of PCs for the year that malaria was eliminated is provided in Figure 42 and Table 15. The first four PCs explain the majority of the dataset, 0.8202 in total, so those PCs were analysed.

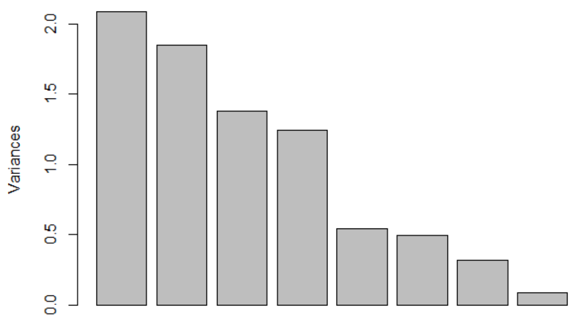
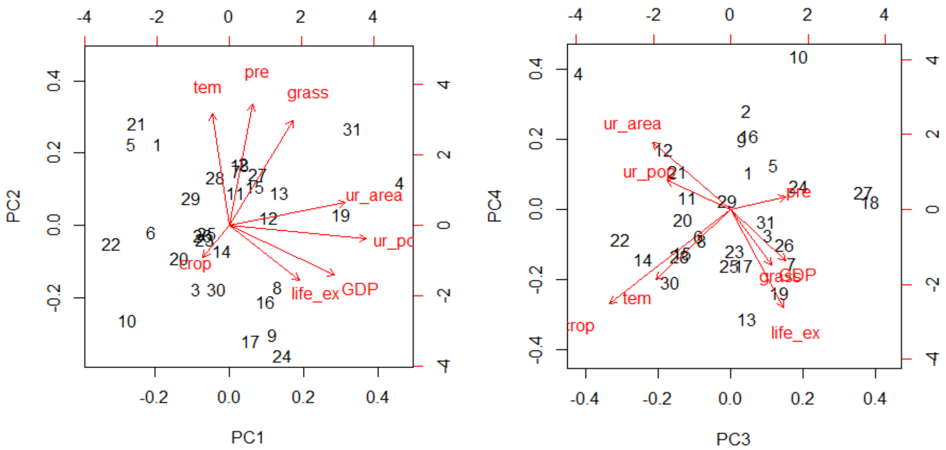


Figure 42. Screeplot of PCA at the time of malaria elimination.

Table 15. Importance of components for the time of malaria elimination.

	PC1	PC2	PC3	PC4
Standard deviation	1.445	1.3607	1.1742	1.1154
Proportion of Variance	0.261	0.2314	0.1723	0.1555
Cumulative Proportion	0.261	0.4924	0.6647	0.8202

Two biplots were generated by displaying PC1 and PC2, PC3 and PC4, as shown in Figure 43. In PC1, variables of GDP, life expectancy and urbanization are correlated, which is similar to the above PCA. But the level of correlations is reduced. In PC3 and PC4, urbanization is in the opposite direction to GDP and life expectancy, which can be explained by the ranges of individual variables. Some countries have relatively low urbanization but their GDP and life expectancy have reached to high levels. Land use and climatic variables showed some associations but not consistent.



(a) (b)

Figure 43. Biplot of (a) PC1 and PC2; (b) PC2 and PC3 at the time of malaria elimination.

4.3 Individual country studies

5 individual European countries were studied in the sub-national scale. Methods used were dependent on the endemicity data available (Figure 13). In the Netherlands, Maxent was used to model the distribution of malaria based on malaria records; in Spain, forward and backward regression and comparison were applied to explore the associations between case numbers and variables. Moreover, in Italy,

Portugal and UK, different variables were compared at mapped time and that malaria was reduced or eliminated.

4.3.1 The Netherlands

Four environmental layers were used for Maxent modelling. These included three continuous variables – population, cropland and grassland; and one categorical variable – urban land (urban area and non-urban area). Climatic variables were excluded because of their small variations within this country and the great impacts on modelling. The predicted malaria occurrence map is presented in Figure 44, with the original occurrence records on top.

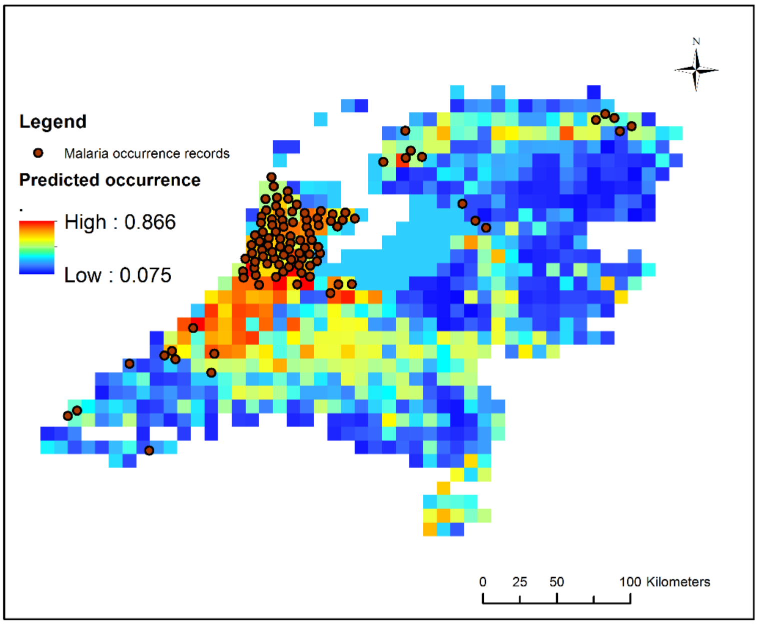


Figure 44. Malaria occurrence map for 1919 the Netherlands predicted in Maxent.

The average AUC value is 0.747 (Figure 45). The importance of each variable to AUC is shown in the jackknife of AUC (Figure 46). It can be seen that malaria distribution in the Netherlands was most associated with cropland and population. Grassland and urban area had limited contribution to the overall prediction.

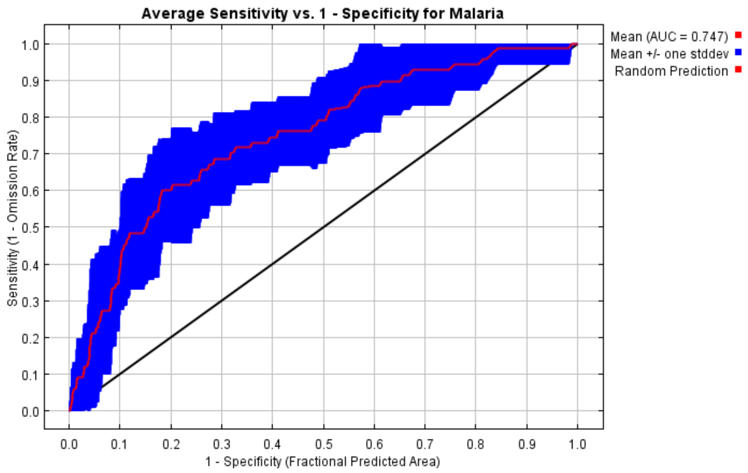


Figure 45. ROC plot of Maxent for the modelling of malaria occurrence in 1919 the Netherlands.

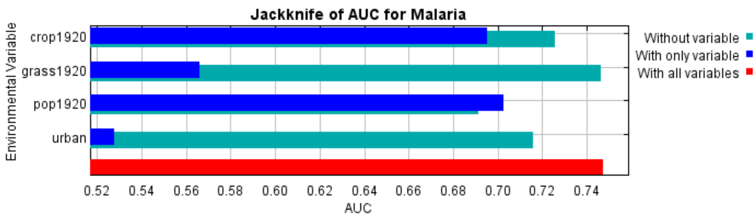


Figure 46. Jackknife of AUC for the modelling of malaria occurrence in 1920 the Netherlands.

4.3.2 Spain

In Spain, regression models were performed in the years of 1920, 1930 and 1950 to detect variables that can best explain the distribution of malaria. From 1950 and 1960, death numbers caused by malaria were greatly reduced and limited to only two provinces. So the changes of variables in 1950 and 1960 were compared at the provincial level.

Regression

Before running regression models, multi-collinearity for each pair of variables was detected by calculating pearsons correlations and VIF. It was found that variables of temperature and frost day frequency were highly correlated in all three time points, so frost day frequency was removed from the list of predictor variables.

Forward and backward selections were performed using the data of case numbers and the rest 6 variables (temperature, precipitation, urban area percentage, urban population percentage, cropland percentage and grassland percentage). Results are shown in Table 16. As can be seen, variables of temperature and cropland percentage were significantly correlated with malaria transmission in 1920, 1930 and 1950. Urban population percentage was correlated with malaria transmission at the year of 1930.

Table 16. Results of regression in 1920, 1930 and 1950 Spain.

Year	Correlated variables	p-value	Adjusted R-squared
1920	temperature	<0.001	0.5146
	cropland	<0.01	
1930	temperature	<0.001	0.5313
	cropland	<0.001	
	urban population	<0.05	
1950	temperature	<0.001	0.5604
	cropland	<0.05	

Comparisons

The changes of variables in 1950 and 1960 are shown in Figure 47-Figure ***53***, with boxplots on the left side and scatterplots on the right side. Scatterplots display the transitions of variables from 1950 to 1960, separated by one-to-one line.

Great increases were seen in the proportions of urban area and population, while the differences in other variables were rather small. Temperature showed no significant change (Wilcoxon test: z=0.011, p=0.994), but frost day frequency had significantly declined (Wilcoxon test: z=5.503, p<0.0001) though the magnitude was small. Another climatic variable precipitation showed certain differences (Wilcoxon test: z=-2.37, p<0.05). Besides, both cropland and grassland had increased (Wilcoxon test: cropland: z=-5.947, p<0.0001, grassland: z=-3.048, p<0.01), but with very small magnitudes.

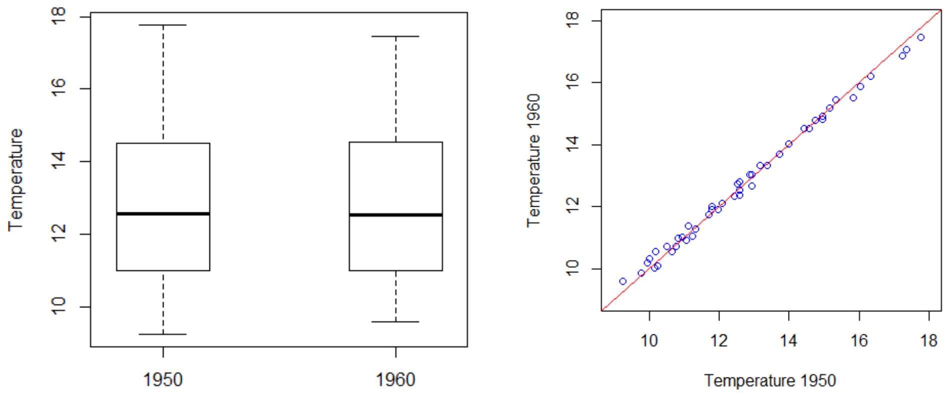


Figure 47. Plots showing the changes of yearly mean temperature in provinces of Spain from 1950 to 1960.

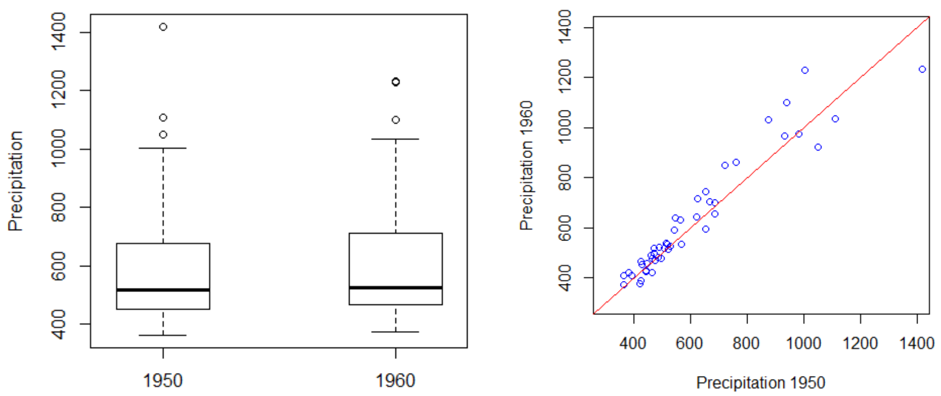


Figure 48. Plots showing the changes of yearly precipitation in provinces of Spain from 1950 to 1960.

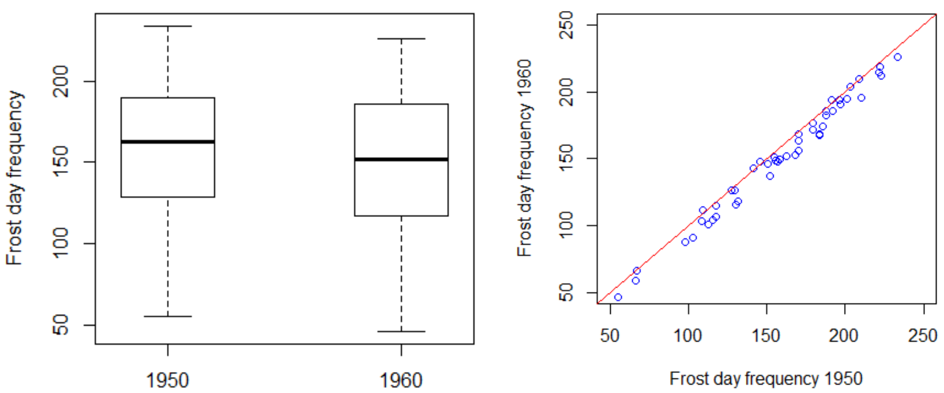


Figure 49. Plots showing the changes of yearly frost day frequency in provinces of Spain from 1950 to 1960.

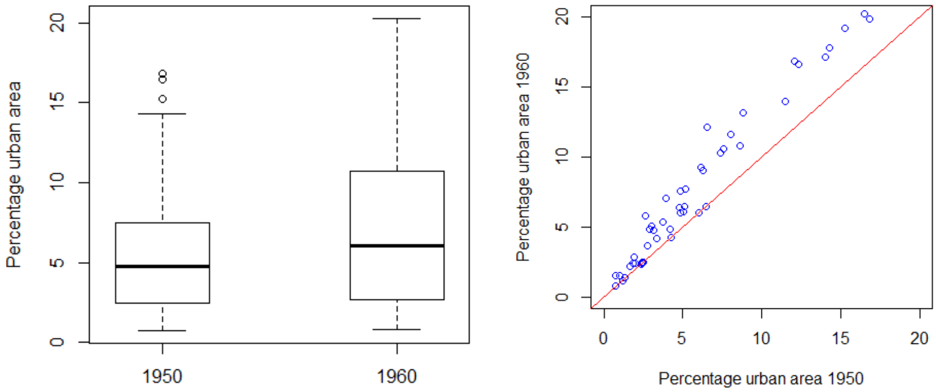


Figure 50. Plots showing the changes of the percentage urban area in provinces of Spain from 1950 to 1960.

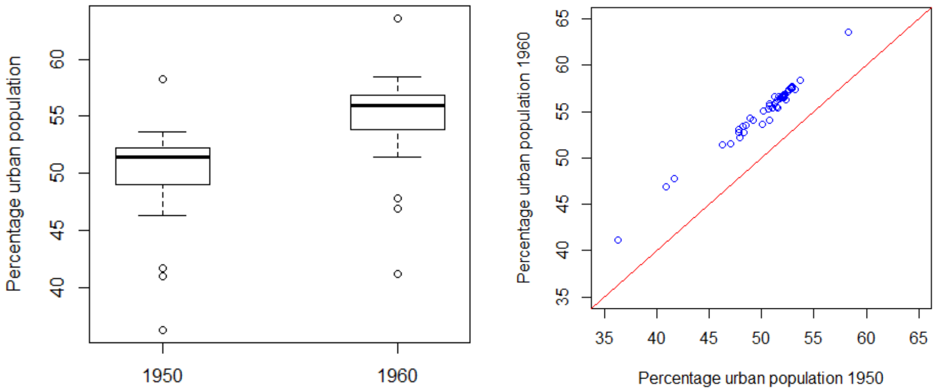


Figure 51. Plots showing the changes of the percentage urban population in provinces of Spain from 1950 to 1960.

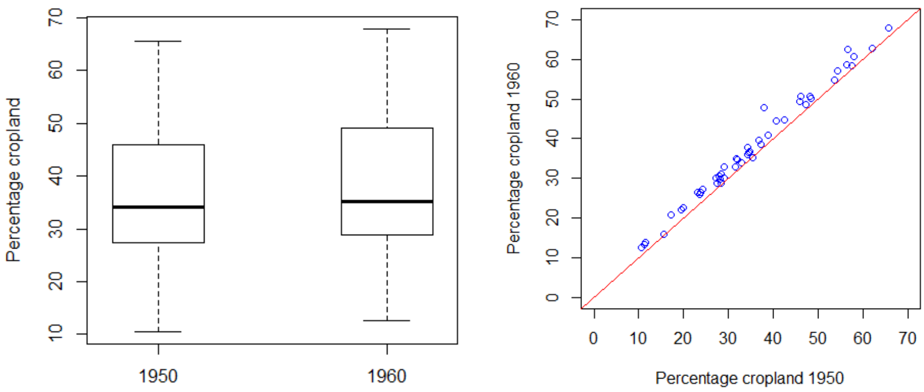


Figure 52. Plots showing the changes of the percentage cropland in provinces of Spain from 1950 to 1960.

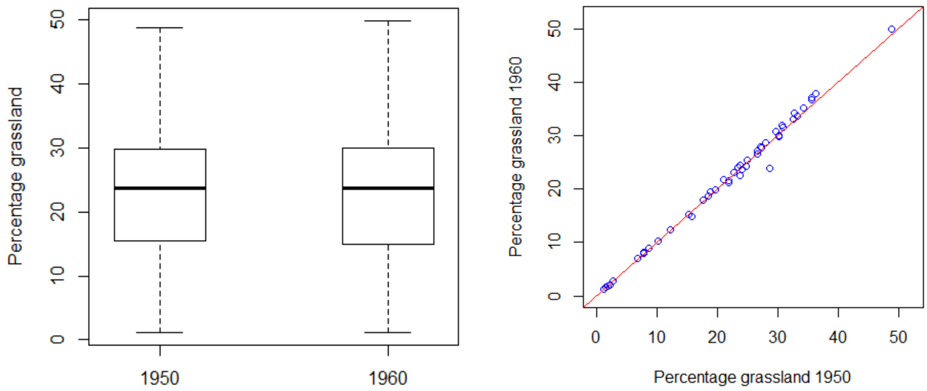


Figure 53. Plots showing the changes of the percentage grassland in provinces of Spain from 1950 to 1960.

4.3.3 Italy, Portugal and Britain

Italy, Portugal and Britain were compared at spatial and temporal dimensions. Spatially, from low to high endemicity levels, the differences of variables were compared. Temporally, variables were compared between the mapped dates and that of malaria elimination (Italy and Portugal) or reduction (Britain). Therefore, Italy was studied in the years of 1946 and 1960, Portugal in 1933 and 1960, and Britain in 1900 and 1920. HYDE variables in 1946 Italy were averaged from the layers of 1940 and 1950. In 1933 Portugal, HYDE datasets in 1930 were used.

Italy

Comparisons of 7 variables in 1946 and 1960 Italy are shown in Figure 54. It is obvious that from non-malaria to high burden of malaria transmission, temperature was increasing; and correspondingly, frost day frequency was decreasing. Besides, precipitation was less in areas with higher endemicity. No consistent pattern was shown in urbanization and land use variables.

From 1946 to 1960, temperature, frost day frequency and grassland remained similar levels. But precipitation, urbanization in both area and population, and cropland had significantly increased.

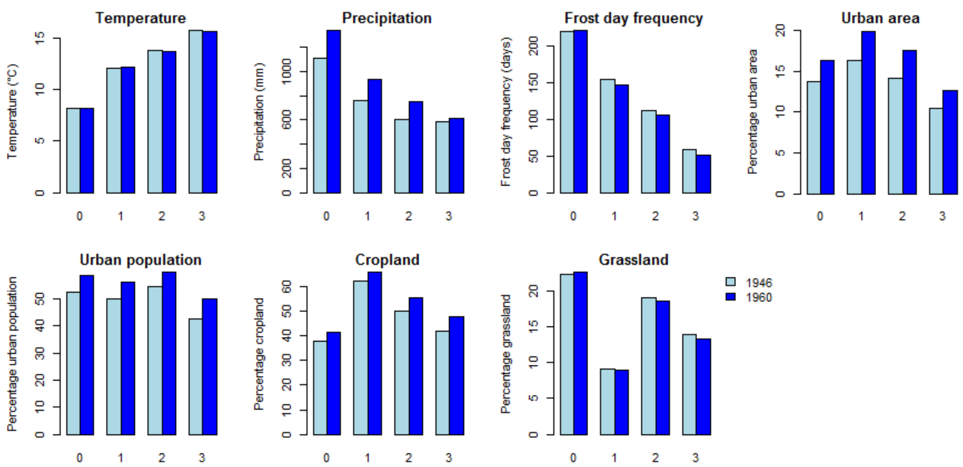


Figure 54. Bar plots showing the differences of variables at different malaria endemicity levels (corresponding to Figure 12 (b), level 0 refers to no malaria and level 3 refers to meso-hyper endemicity) and the changes from 1946 to 1960 in Italy.

Portugal

For Portugal, comparisons of variables in 1933 and 1960 are presented in Figure 55. Spatially, there was no consistent pattern shown. Temporally, all variables had increased significantly, especially urban area and population. Surprisingly, with about 1◦C temperature rise, frost day frequency reduced about 25 days, meaning that frost day frequency was very sensitive to temperature increase.

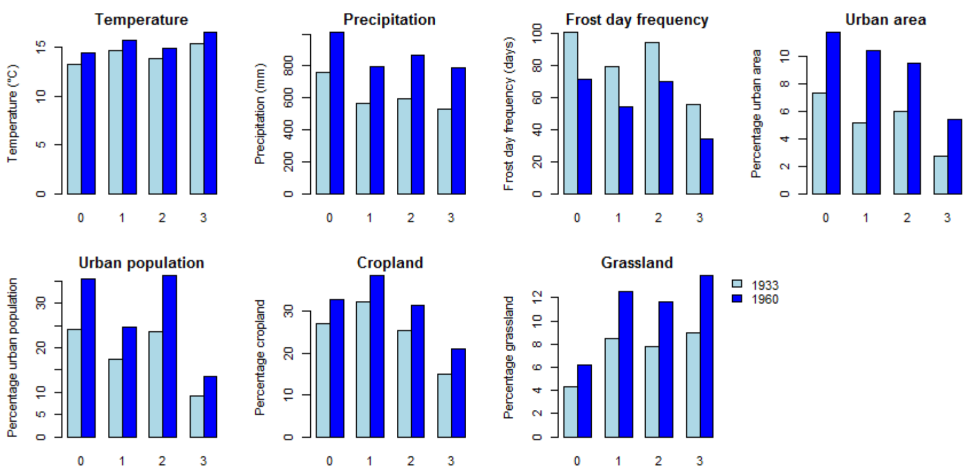


Figure 55. Bar plots showing the differences of variables at different malaria endemicity levels (corresponding to Figure 12 (a), level 0

refers to the lowest splenic index and level 3 refers to the highest splenic index) and the changes from 1933 to 1960 in Portugal.

In Britain, comparisons of variables between 1900 and 1920 are shown in Figure 56. As can be seen, areas with high malaria endemicity had roughly more cropland and less grassland. Differences in other variables were not consistent or significant. Temporally, increases in urbanization, cropland and grassland were seen.

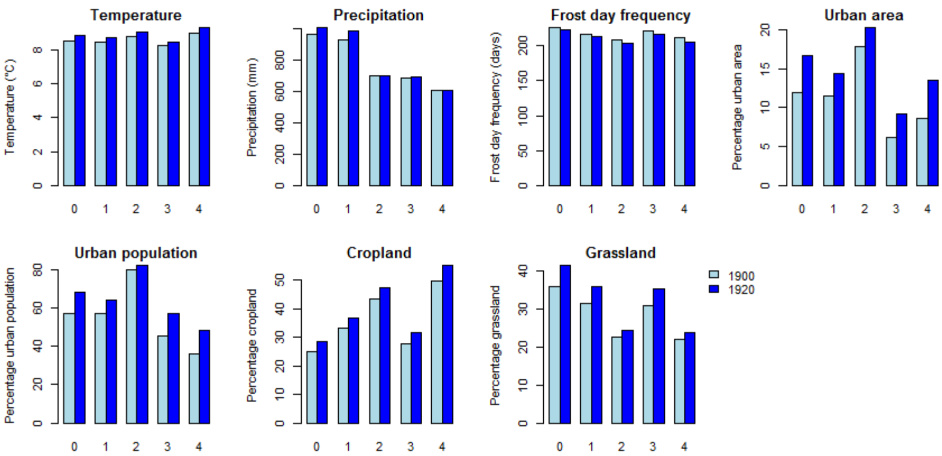


Figure 56. Bar plots showing the differences of variables at different malaria endemicity levels (corresponding to Figure 12 (d), level 0 refers to the lowest malaria death rates and level 4 refers to the highest malaria death rates) and the changes from 1900 to 1920 in Britain.

4.4 Comparisons with malaria eliminating countries

Current malaria eliminating countries were compared with 31 European study countries by climatic variables, GDP, life expectancy, urbanization and land use variables. The time for eliminating countries was 1900 and 2000 (2012 for GDP and life expectancy) – the start time of comparison and the contemporary time; while that for Europe was 1900, malaria with large drop and malaria eliminated. The aim of those comparisons was to see if they were different in 1900, and how close current eliminating countries were to Europe at the time of malaria with large drop and that of malaria elimination.

4.4.1 Climatic variables

Comparisons of climatic variable showed that eliminating countries had higher temperature and less frost day frequency than the 31 post-elimination European countries. Moreover, yearly precipitation was similar in those two types of countries.

Temperature

As shown in Figure 57, temperature in current eliminating countries was significantly higher than that in European countries (Mann-Whitney test, 1900: z=-5.057, p<0.0001; malaria with large drop in Europe versus eliminating countries in 2000: z=-5.057, z=p<0.0001; malaria eliminated in Europe versus eliminating countries in 2000: z=-4.965, p<0.0001). During the one hundred years of climate change, those still endemic countries have seen significant temperature increase (Wilcoxon test: z=-4.984, p<0.001), although the magnitude was relatively small.

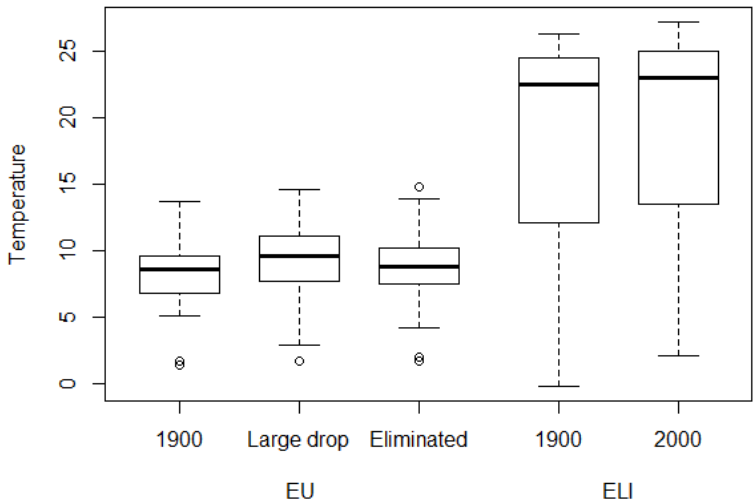


Figure 57. Boxplots showing the differences in yearly mean temperature between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

Precipitation

Figure 58 displays the variations of precipitation in Europe and current eliminating countries. By statistical test, precipitation in Europe and eliminating countries was no difference (Mann-Whitney test, in 1900: z=-0.854, p=0.3994; malaria with large drop in Europe versus eliminating countries in 2000: z=-1.524, p=0.1229; malaria eliminated in Europe versus eliminating countries in 2000: z=-0.933, p=0.357). From 1900 to 2000, eliminating countries had increased precipitation (Wilcoxon test: z=-3.257, p<0.005), but the magnitude was small.

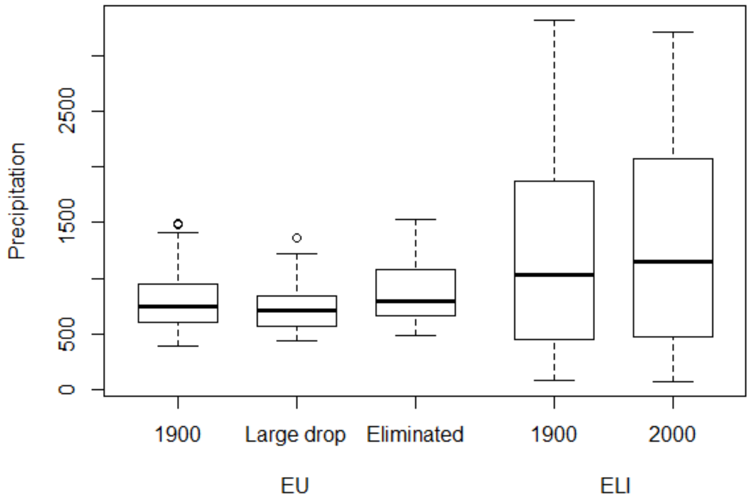


Figure 58. Boxplots showing the differences in yearly precipitation between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

Frost day frequency

As an alternative indicator of temperature, frost day frequency shows inverse values to temperature, as seen in Figure 59. Current malaria eliminating countries had much less frost days than European countries in each pair of comparison (Mann-Whitney test, 1900: z=4.295, p<0.0001; malaria with large drop in Europe versus eliminating countries in 2000: z=4.623, p<0.0001; malaria eliminated in Europe versus eliminating countries in 2000: z=4.755, p<0.0001). During last century, frost day frequency had decreased significantly (Wilcoxon test: z= 5.001, p<0.0001), with small scales though.

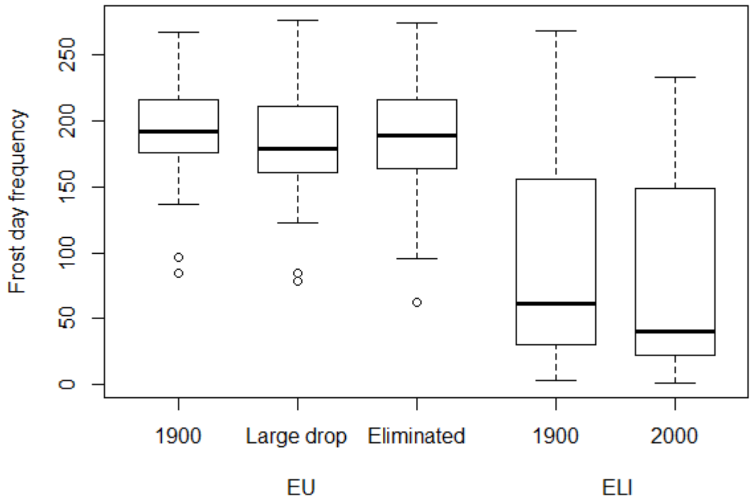


Figure 59. Boxplots showing the differences in yearly frost day frequency between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000)

4.4.2 GDP per capita and life expectancy

GDP per capita and life expectancy in 1900 and 2012 eliminating countries were compared with Europe at the three time points. Results showed that both variables were lower in eliminating countries than Europe in 1900, but by 2012 eliminating countries had caught up with Europe at the time of malaria elimination.

GDP per capita

Comparisons of GDP per capita in European countries and current eliminating countries are shown in Figure 60. In 1900, eliminating countries had lower income than European countries (Mann Whitney test: $z=-4.886$, $p<0.0001$). After one hundred years economic development, eliminating countries had significant increases in GDP (Wilcoxon test: $z=-5.086$, $p<0.0001$), exceeding Europe at the time of malaria with large drop (Mann Whitney test: $z=3.678$, $p<0.001$). In 2012, eliminating countries had achieved the same level of GDP per capita as Europe at the time that malaria was elimination was eliminated (Mann Whitney test: $z=-0.657$, $p=0.581$).

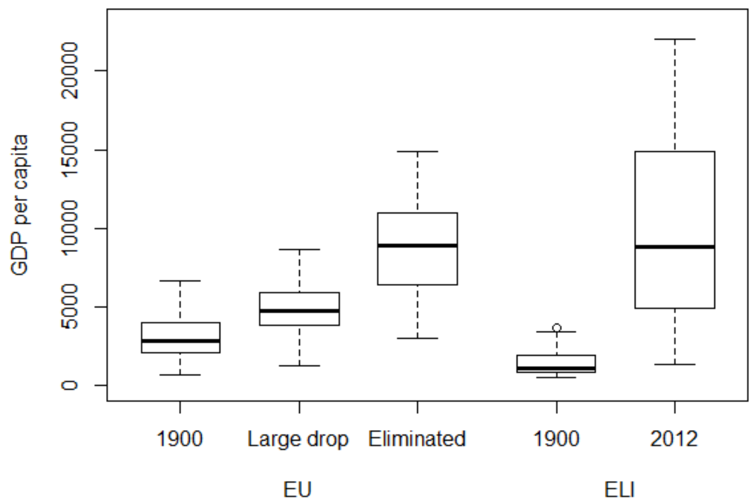


Figure 60. Boxplots showing the differences in GDP per capita between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2012).

Life expectancy

As shown in Figure 61, life expectancy in eliminating countries had great increases during last century (Wilcoxon test: $z=-5.086$, $p<0.0001$). In 1900, eliminating countries had lower life expectancy than Europe (Mann Whitney test: $z=-6.377$, $p<0.0001$). But by 2012 life expectancy in eliminating countries had been significantly higher than that in Europe at the time of malaria elimination (Mann Whitney test: $z=-3.442$, $p<0.001$).

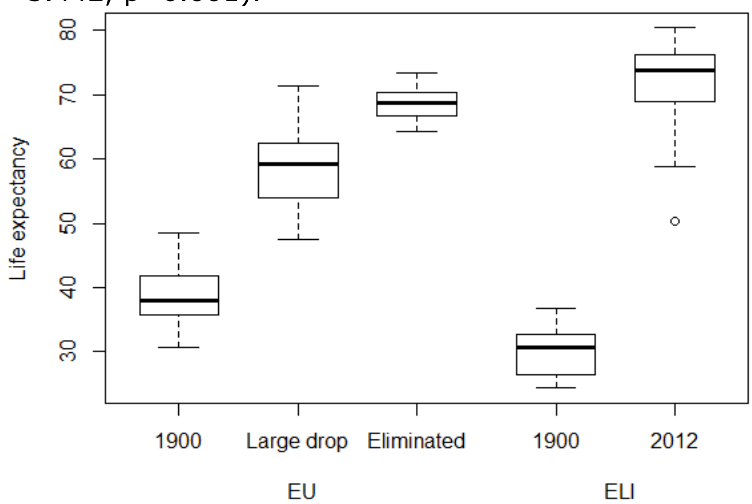


Figure 61. Boxplots showing the differences in life expectancy between 31 European countries (in the years of 1900, malaria with

large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2012)

4.4.3 Urbanization

Both percentages of urban area and urban population in eliminating countries have achieved the same levels as European countries at the time of malaria elimination.

Urban area

The differences in the urban area percentage betwen Europe and eliminating countries across last century are shown in Figure 62. In 1900, all countries had low proportions of land urbanized, but values in Europe were higher than that in eliminating countries (Mann Whitney test: $z=2.929$, $p<0.05$). After the rapid development of one century, urban area in eliminating countries had significantly increased (Wilcoxon test: $z= -4.915$, $p<0.0001$), arriving the same level as Europe at both the time of malaria with large drop (Mann Whitney test: $z=-1.235$, $p=0.221$) and elimination (Mann Whitney test: $z=0.854$, $p=0.399$).

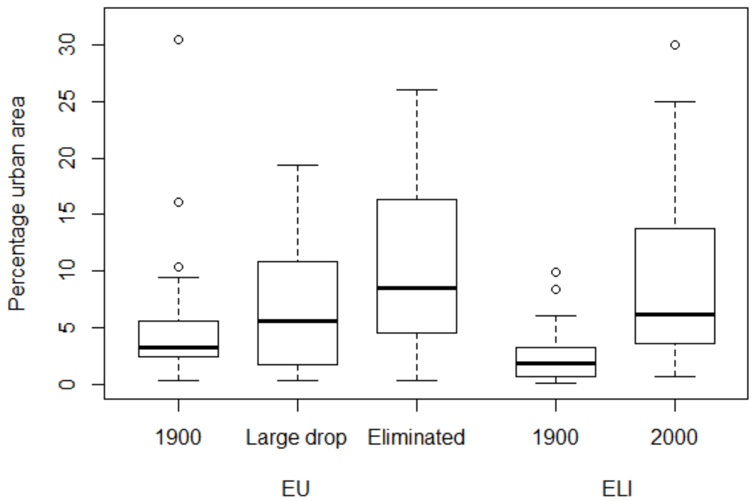


Figure 62. Boxplots showing the differences in the percentage urban area between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

Urban population

Along with the growth of urbanized area, urban populations in eliminating countries had also significantly increased during last century (Wilcoxon test: $z=-5.086$, $p<0.0001$), as shown in Figure 63. At the beginning of 20th century, urban populations in eliminating countries was similar to that in European countries (Mann Whitney test: z=1.445, p=0.151). In 2000, the rates of urbanized populations in eliminating countries were higher than Europe at the large drop of malaria (Mann Whitney test: z=-2.758, p<0.05) and very similar to Europe at the time that malaria elimination was achieved (Mann Whitney test: z=0.013, p=0.995).

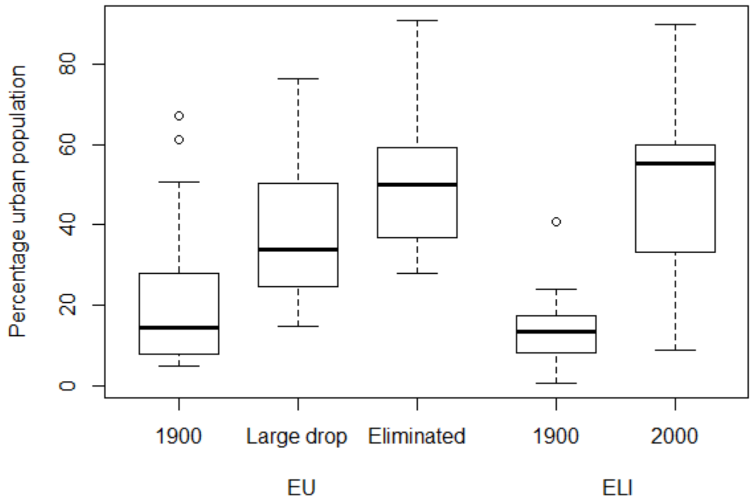


Figure 63. Boxplots showing the differences in the percentage urban population between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

4.4.4 Land use change

Both the percentages of cropland and grassland had greatly increased in malaria eliminating countries during last century. Comparing with Europe at different stages of malaria reduction, eliminating countries had lower cropland percentages and similar rates of grassland.

Cropland

The changes in the percentage of cropland in Europe and eliminating countries are presented in Figure 64. Originally, eliminating countries had lower rates of cropland than European countries (Mann-Whitney test: z=6.199, p<0.0001). During last century, cropland in eliminating countries had considerably increased (Wilcoxon test: z=4.505, p<0.001), but still lower than Europe at both time of malaria with large drop and elimination (Mann-Whitney test: z=4.82, p<0.0001).

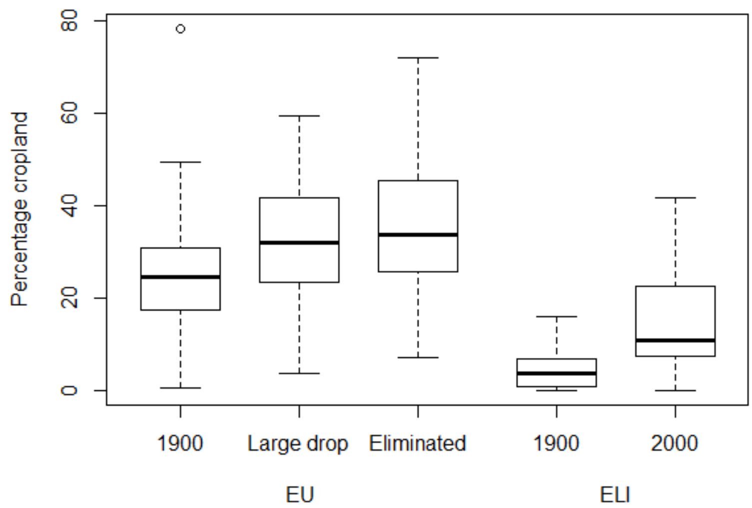


Figure 64. Boxplots showing the differences in the percentage cropland between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

Grassland

Figure 65 shows the changes in the grassland percentage in European countries and malaria eliminating countries. In 1900, eliminating countries had lower rates of grassland than Europe (Mann-Whitney test: $z= 3.047$, $p<0.01$). From 1900 to 2000, grassland in eliminating countries had significantly increased (Wilcoxon test: $z=-5.08$, $p<0.0001$). Despite the wide range of the grassland percentages in eliminating countries, statistical tests showed that there was no much difference between eliminating countries and European countries (Mann-Whitney tests, eliminating countries in 2000 versus Europe at the large drop of malaria: $z=-0.906$, $p=0.371$; eliminating countries in 2000 and Europe at the elimination of malaria: $z=0.788$, $p=0.437$).

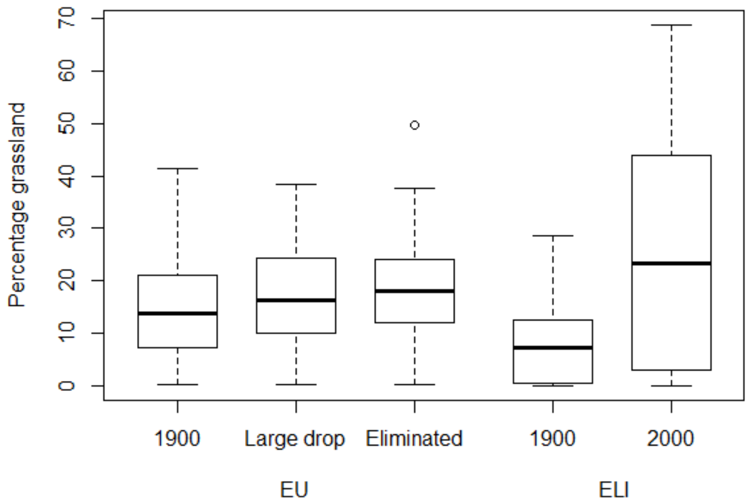


Figure 65. Boxplots showing the differences in the percentage grassland between 31 European countries (in the years of 1900, malaria with large drop, and malaria eliminated) and current malaria eliminating countries (in 1900 and 2000).

5 Discussion

In this study, the associations between malaria reductions and different variables were quantitatively examined in space and time. The elimination of malaria in Europe was likely the combined effects from both favourable and unfavourable factors. However, it remains challenging to measure the magnitudes of the positive or negative effects from each factor.

5.1 Drivers of malaria elimination in Europe

In Europe, candidate variables were analysed at different geographical scales. Variables of temperature and cropland were found to be highly correlated with malaria transmission. But the elimination of malaria was probably driven by the socio-economic development and the related changes that irreversibly reduced the receptivity of malaria in those countries.

5.1.1 Regional scale

High temperature favours malaria transmission. This can be seen from the spatial comparisons, that malaria endemic areas had much higher temperature than those eliminated. But the changes of temperature over time were so small comparing with the spatial differences, that climate warming had limited influences on malaria transmission. Thus other factors should be considered (Gething et al., 2010).

Frost day frequency was an alternative indicator to temperature, so it showed the similar trend. Areas with long winter periods eliminated malaria earlier than those with relatively short winter time. The temporal changes of frost day frequency were much smaller than the spatial differences, which was the same to temperature.

In contrast to earlier findings, however, the regional comparisons of precipitation were not able to support previous studies. Normally, high precipitation means more breeding sites for mosquitoes and thus supports malaria transmission (Kuhn et al., 2003; Reiter, 2001). But here, areas eliminated malaria presented higher precipitation than those still endemic. And temporal comparisons showed either no change or certain increases in precipitation. This confliction might be because the local water storage, such as rivers, lakes, channels and so on had more impacts on local water supply. Or probably the topography, landscape or water management had a greater effect on the duration of rainfall on the ground. It might also be the results of the overly generalized datasets, which was at a large spatial scale.

Both urbanization and land use data were crudely aggregated, but the general trends were revealed. Urbanized area and population had greatly increased during studied period in Europe, indicating the rapid demographic transitions and economic development. The increases in cropland and grassland were expected when considering the exponential population growth. But the results from spatial and temporal comparisons need more evidences from smaller scale analysis.

5.1.2 National scale

The basis of national comparisons were the segmented stages of malaria declines over time, which had predefined that only variables with consistent changes might be the drivers of malaria elimination in Europe.

For climatic variables, irregular patterns were shown. On one hand, this reconfirmed that the temporal changes in climate were unlikely to have made much impact on malaria elimination, as seen in regional comparisons. On the other hand, the rises and falls of temperature seem to go against the global warming trend and the regional comparisons. However, certain fluctuations were inherent in climatic variables and regional comparisons showed that the changes in temperature from 1946 to 1975 were smaller than that from 1900 to 1946. Besides, the dates of malaria with large drop and malaria eliminated were different by country, and this might have caused some coincidence.

Variables of GDP per capita, life expectancy and urbanization had continuously increased during the decline of malaria in Europe. Thus those variables were very likely to be the main drivers of malaria elimination in Europe. These findings quantitatively support previous researches that malaria decline or elimination were related to greater wealth (Feachem et al., 2010), higher urbanization rates (Robert et al., 2003; Tatem et al., 2013) and better access to healthcare facilities (Hay et al., 2005). In addition, results of PCA in all three time points implied high correlations among these factors, which means that wealthy countries also had better health status and higher rates of urbanization. As those variables are all about socio-economic development, if the associations could be extrapolated, then other related factors, such as better housing quality, nutritious conditions and living environments (Dobson, 1980) might also have played a part in malaria elimination. In Finland, this improvement was revealed by reduced family size and better housing quality (Hulden & Hulden, 2009). Overall, the elimination of malaria tend to be the result of progressive improvements in socio-economic developments (James, 1929; Smith et al., 2013).

The effects of crop and grass land use change were not clear in the national-scale comparisons, as major increases in both percentages of cropland and grassland were in the early period of malaria decline, while no much change was seen in the later time.

5.1.3 Individual country studies

Individual country case studies allowed a detailed look at the relationships between malaria endemicity and factors. Results showed that the distribution of malaria in those countries was mostly associated with temperature and cropland. Here, the differences can be seen by the size of the country. In relatively small countries like the Netherlands and Britain, the effects of temperature were not obvious, but the associations with crop cultivation were high. In large countries like Italy, temperature was the dominant factor affecting malaria transmission, but no consistent pattern was seen related to the cropland percentage. While in Spain malaria cases were correlated with both temperature and the cropland percentage. In total, the impact of temperature on malaria transmission was in line with regional comparisons, but the relevance with the percentage of cropland was not shown in either regional or national comparisons. This is probably because the aggregation of cropland datasets smoothed the contrast within regions or nations. Furthermore, cropland were likely to have connections with water bodies, for irrigation use. Thus, these findings match earlier studies suggesting the linkage between malaria and water bodies (Dobson, 1980; Majori, 2012; Sousa et al., 2009; Arturo Sousa et al., 2014). However, these associations were not shown in Portugal, possible explanation might be the unbalanced areas in comparisons – no or low-transmission areas took up the majority of the whole country and the highly endemic areas had small proportions.

Temporally, the reductions of malaria were associated with the increases in urbanization. The typical case was Spain. With other variables almost no change, both the proportions of urban area and population had greatly increased. If the correlations among GDP, life expectancy and urbanization seen from national comparisons were also true here, then the growth in urbanization also indicated the improvement in wealth, healthcare system and housing quality and so on. Therefore the reduction of malaria was probably because the effects of those improvements exceeded that from temperature and cropland.

5.1.4 Combined effects

The connections between malaria transmission cycle and external environments (Smith et al., 2014) determined the complicity of factors driving malaria elimination. This study showed some interesting patterns. First, countries or regions were different at the baseline levels, recognized in Europe as temperature and water bodies. Both factors favoured malaria transmission and thus could increase the difficulty of malaria elimination. Besides, temperature tended to make a difference at a large spatial scale, but the effects of water bodies were relatively local. Second, the gradual disappearance of malaria in Europe was associated with the progressive improvements related to socio-economic developments. Those changes might have led to the permanent alteration in malaria receptivity, so that even though the control measures were withdrew, the elimination state remained. Third, it could be assumed that the elimination of malaria was the combined effects from both categories of factors that favouring malaria transmission and that having a depressing force. If the assumption was true, then when the depressing forces exceeded the favourable effects, malaria started to decline. Finally, factors might have different dynamic characters. For example, the changes of temperature were much slower than the growth in urbanization or transitions in land use.

5.2 Implication for endemic countries

The comparisons of different variables between European countries and current eliminating countries were of great interest. From the comparisons within Europe, it has been found that high temperature was favourable to malaria transmission, and socio-economic factors were the possible drivers of malaria elimination. This was further confirmed by the comparisons with eliminating countries, which had reached similar levels of GDP, urbanization and even higher level of life expectancy relative to Europe at the time that elimination was achieved. But those countries still had ongoing malaria transmission. Probably, the higher temperature and shorter winter time in those eliminating countries added more difficulty in malaria elimination. Therefore, to eliminate malaria in current low-transmission countries, higher socio-economic development might be required. Furthermore, if the findings were indicative, tropical countries with even higher temperature than eliminating countries would need greater improvements in socio-economic developments to achieve elimination. But at the same time most African countries were among the under-developed countries, this contrast may explain why malaria transmission was so ‘sticky’ in those countries.

These findings might be helpful for endemic countries. Firstly, as endemic countries are making great progresses in controlling malaria (WHO, 2014), countries considering moving from controlled low-transmission to elimination were recommended to assess the feasibility of elimination (Feachem et al., 2010). Evidences found in this study might provide indications for feasibility assessment as well as monitoring the progresses towards elimination. Secondly, current control measures mainly focused on the use of ITNs, IRS and treatments (WHO, 2014). However, social and environmental impacts on malaria and other infectious diseases have been ignored. Improvements in housing quality, healthcare facilities, land planning and water management especially for agriculture cultivation might be of great use for controlling malaria. But the specific local situations should be considered.

5.3 Implication for modelling

Substantial efforts have been made towards present and future changes in malaria distribution and intensity. Many of them (Craig et al., 1999; P. Martens et al., 1999; Patz & Olson, 2006; Rogers & Randolph, 2000; Tanser et al., 2003) were based on the scenarios of climate change, mainly temperature and precipitation, while other factors remained constant or had a negligible effect. However, findings in this study showed that the temporal changes of temperature were very small, whereas other factors related to socio-economic developments had great impacts on malaria. Therefore those factors might need more attention than climate change with regard to malaria modelling.

5.4 Limitations

Clearly, various sources of uncertainties exist in the input datasets and methodology used in this study. For malaria endemicity data, malaria maps extracted from the global ones (Figure 6) were plausible when comparing with the dates of elimination reported for European countries, putting a limitation on using them at national or sub-national scales. Other malaria endemicity data or maps had different formats, dates and construction criteria, and unknown accuracy. For candidate variables, some other indicators, such as cattle numbers, physicians, or health expenses might also be desirable, but those datasets were not available for a hundred years ago. Moreover, the existing datasets were made from incomplete sources, and contained different levels of assumptions and modelling, which affected the reliability of the datasets used.

The methodology applied was greatly compromised with the availability and quality of the existing data, but this caused some side effects. First and foremost, the variables and methods used for different scale comparisons were not consistent. One obvious example is that the variables of GDP per capita and life expectancy were only compared at the national scale, not at the regional or individual country scales. Besides, variables were largely or even overly aggregated to either average or proportional values, especially urbanization and land use data for comparisons at the regional scale. This might have resulted in loss of information.

6. Conclusions

Here, the driving forces of malaria elimination in Europe were systematically quantified in space and time for the first time. Malaria elimination in Europe seems to be the combined effects from both favourable and unfavourable factors. The declines of malaria in Europe were highly coincident with socio-economic developments, including increased wealth, urbanization, improved health system, better sanitation condition and housing quality and so on. Besides, high temperature favours malaria transmission, but the changes in temperature during last century might not have made much difference, because the magnitudes of temperature changes were very small when compared with spatial differences.

Comparisons between European countries at different stages of malaria decline and current eliminating countries, suggest that eliminating countries have reached similar levels of socio-economic developments to Europe at the time of elimination, but the higher temperature and shorter winter periods in those still endemic countries tend to imply higher thresholds to accomplish the final elimination of malaria.

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Appendix

Start dates of national wide anti-malaria programs, dates of last indigenous malaria cases and dates of WHO certified or added as malaria-free countries in Europe.

Country	Start date of national wide anti-malaria program	Date of last indigenous case	Date of WHO certified or added as malaria-free countries
Albania	1947	1966	2012
Austria			1963
Belarus	1951		2012
Belgium		1938	1963
Bosnia and Herzegovina	1947	1964	1973
Bulgaria	1947-1950	1957(*pf*); 1960(*pv*)	1965
Croatia	1947	1964	1973
Czech Republic			1963
Estonia	1951		2012
Finland		1954	1963
France		1950	2012
Germany		1950	1964
Greece	1946-1954	1973	2012
Hungary	1946	1962	1964
Italy	1930s large-scale land reclamation and sanitation; 1944-1945 DDT spaying	1952(*pf*); 1962(*pv*)	1970
Latvia	1951		2012
Lithuania	1951		2012
Montenegro	1947	1964	1973
Netherlands	1946	1961	1970
Poland	After WW1 health regulations were	1955	1967

	applied; 1945 national wide plan.		
Portugal	1930s intensive control measures; 1948 DDT spraying and new anti-malaria drugs	1958	1973
Republic of Moldova	1951		2012
Romania	1949	1962	1967
Russian Federation	1951		2012
Serbia	1947	1964	1973
Slovakia			1963
Slovenia	1947	1964	1973
Spain	From 1943, 330 anti-malaria dispensaries were established	1962	1964
The former Yugoslav Republic of Macedonia	1947	1964	1973
Ukraine	1951		2012
United Kingdom of Great Britain and Northern Ireland	After WW1, malaria surveillance and treatment were applied	1953	1963