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DEVELOPMENT OF A NEW MODEL FOR EVALUATING MALARIA RISK IN CHIMOIO, MOZAMBIQUE

Sofia Damiana Vieira da Luz Gouveia

Dissertation presented as partial requirement for obtaining the Master's degree in Information Management

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by

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Advisor: Professor Doutor Jorge M. Mendes

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ABSTRACT

Malaria is a life-threatening disease that continues to pose serious economic, social and health burdens. Climate plays an important role in the dynamics and distribution of malaria. In particular, temperature and precipitation appear to be critical in perpetuating malaria transmission. In the last decades, there has been an increased interest in the use of weather forecasts for predicting malaria epidemics and setting up early warning systems.

In 2017, there have been almost 9 million reported cases of malaria in Mozambique. Malaria is considered one of the deadliest diseases in the country. Previous studies have established that temperature, rainfall and humidity were determinant for malaria transmission and intensity in this region. The purpose of this study is to apply time series analysis and regression modelling to analyse the relationship between malaria incidence and these climatic variables in Chimoio, a municipality located in central Mozambique, and possibly develop a model that can accurately predict the occurrence of malaria outbreaks across this region.

With a combination of two (15-week lagged maximum temperature and 3-week lagged precipitation) to three (15-week lagged maximum temperature, 12-week lagged relative humidity and 3-week lagged precipitation) climatic variables, added to the number of malaria cases reported in the previous week, we were able to explain more than 70% of the variability in weekly malaria incidence. These models also quite accurately represent the observed trends of malaria incidence in Chimoio, during the study period.

This simple and economical approach, supported by meteorological and epidemiologic data that are readily available, could potentially be applied by local health authorities in order to predict malaria outbreaks. With this information, adequate preventative interventions and resource allocation could be planned and deployed within a more reasonable time frame.

Further studies are required in order to determine if this methodology can be successfully applied to other regions of the globe.

KEYWORDS

Generalized Additive Models; Malaria; Relative Humidity; Precipitation; Temperature.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIC	Akaike's Information Criteria
ARIMA	Autoregressive Integrated Moving Average
BIC	Bayesian Information Criteria
CAR	Conditional Auto-Regressive
CDC	Centers for Disease Control and Prevention
DLNM	Distributed Lag Nonlinear Model
ENSO	El Niño Southern Oscillation
EVI	Enhanced Vegetation Index
GAM	Generalized Additive Model
GAMM	Generalized Additive Mixed Effects Model
GEE	Generalized Estimating Equation
GLM	Generalized Linear Model
GLMM	Generalized Linear Mixed Model
GLS	Generalized Least Square
INE	Instituto Nacional de Estatística
IOD	Indian Ocean Dipole
LMM	Liverpool Malaria Model
MAE	Mean Absolute Error
Mal_1	number of malaria cases observed in the previous week
MCMC	Markov Chain Monte Carlo
MAPE	Mean Absolute Percentage Error
NVDI	Normalized Difference Vegetation Index
P	Precipitation
RH	Relative Humidity
RMSE	Root Mean Square Error

SARIMA Seasonal Autoregressive Integrated Moving Average

SST Sea Surface Temperature

SWS Soil Water Storage

Tmax Maximum Temperature

Tmean Mean Temperature

Tmin Minimum Temperature

WHO World Health Organization

ZMIS Zambia National Malaria Indicator Survey

1. INTRODUCTION

Malaria is a life-threatening disease that continues to pose serious economic, social and health burdens. According to World Health Organization's (WHO) World Malaria Report for 2019, an estimated 228 million cases of malaria occurred worldwide during the year 2018, most of them (93%) in Africa.

Malaria is caused by a protozoan parasite belonging to the genus Plasmodium. The parasite requires two hosts to complete its life cycle: a female Anopheles mosquito (the vector, whose bites are the mode of transmission of the parasite between human hosts) and a human (CDC, 2018b).

Climate plays an important role in the dynamics and distribution of malaria. Factors such as temperature, humidity, precipitation (or rainfall) and wind patterns can significantly impact both vector and parasite's development, reproduction and survival, therefore influencing its capacity to infect human hosts (Mandal, Sarkar, & Sinha, 2011).

Adequate temperature and precipitation appear to be critical in perpetuating malaria transmission, having been identified as significant drivers of malaria disease considerably more than any other climatic variable (Reiner et al., 2015).

Temperature can significantly alter the rate of mosquito's development, breeding and survival, as well as its biting rate. In addition, the parasites' development rate and survival within the mosquito also depends on environmental temperature (Blanford et al., 2013).

On the other hand, precipitation is critical in providing stagnant water bodies, which are the most suitable habitats for mosquitoes to reproduce. As rainfall can significantly alter the sustainability of the mosquito population, the seasonality of malaria transmission is mostly driven by the annual cyclical changes in rainfall patterns (Morse et al., 2005; Parham & Michael, 2010).

One of the earliest mathematical models of malaria transmission, the Ross model, was published in the early 1900 (Ross, 1911). Since then, many other models have been developed, introducing further explanatory variables and progressively increasing the complexity of interactions between them, in an attempt to obtain a more realistic and precise representation of the disease (Mandal et al., 2011).

Following the El Nino phenomenon, which in 1998 was responsible for a major malaria outbreak (Brown et al., 1998), the scientific community showed an increasing interest in the use of weather forecasts for predicting malaria epidemics and setting up early warning systems (Githeko & Ndegwa, 2001; WHO, 2001).

In 2017, there have been almost 9 million reported cases of malaria in Mozambique, which means that this disease affected at least 30% of the country's population (WHO, 2018). Malaria is considered one of the most deadly diseases in the country and is also the leading cause of death among hospitalized children in Mozambique (Zacarias & Andersson, 2010).

Previous authors have established that several climatic features (temperature, rainfall and humidity) were determinant for malaria transmission and intensity in this country (Zacarias & Andersson, 2011).

Chimoio is a municipality located in the Manica Province, in the central region of Mozambique, with an area of 174 km^2 at an altitude of 750 m. Chimoio has a warm temperate climate with dry winters from April to July, hot and dry summer from August to October, and hot humid summer from November to March (Ferrão et al., 2016).

Annual malaria cases have been increasing in Chimoio since 2010 (Ferrão et al., 2016), which is contrary to the overall decreasing trend observed in Africa, in the same period (WHO, 2015b). The highest number of cases occurs in February (peak of the rainy season) and the lowest in September, during the dry season. Malaria mortality rates are significantly higher in January, February and March. The seasonality of malaria incidence and mortality in Chimoio has been associated with temperature and rainfall (Ferrão, Mendes & Painho, 2017a; Ferrão et al., 2017b).

1.1. STUDY OBJECTIVES

The purpose of this study is to revisit the dataset analysed by Ferrão et al. (2017a), which contains weekly data from a nine-year period (2006 to 2014), collected in the Chimoio district.

The available variables are the number of reported malaria cases, minimum, maximum and mean temperature (°C), relative humidity (%) and precipitation (mm).

By applying time series analysis and regression modelling, we intend to further explore the relationship between malaria incidence and selected climatic variables (temperature, humidity and precipitation) and possibly develop a model that, based on these readily available features, can accurately predict the occurrence of malaria outbreaks across the Chimoio region.

Considering that this type of climatic data can easily be obtained, this model could potentially be employed by health authorities in order to predict malaria outbreaks and allocate adequate resources.

As part of the exploratory data analysis, the secondary objectives would be to:

- Establish which subset of climatic variables generates the better representation on the evolution of weekly malaria incidence in this region.
- Determine which is the best metric to represent the influence of temperature on malaria transmission, i.e., if among the range of different temperatures available (minimum, maximum and mean temperature) there is one that provides more accurate results.

2. LITERATURE REVIEW

Malaria is a life-threatening disease that continues to pose serious economic, social and health burdens.

According to the WHO's World Malaria Report for 2019, an estimated 228 million cases of malaria occurred worldwide during the year 2018, most of them (93%) in Africa. In addition, from the estimated 405.000 global annual deaths attributed to malaria, 94% also took place in the WHO African Region.

In particular, six countries located in sub-Saharan Africa accounted for more than half of all reported malaria cases: Nigeria (25%), the Democratic Republic of the Congo (12%), Uganda (5%) Côte d'Ivoire, Mozambique and Niger (4% each).

Despite significant global monetary investments allocated to malaria control and elimination efforts, there has been no significant progress in reducing malaria incidence since 2014 (WHO, 2019).

One of the pillars of the WHO's Global technical strategy for malaria 2016–2030 (WHO, 2015a) is to transform malaria surveillance into a core intervention. In order to achieve this goal, effective surveillance systems that can collect data regarding malaria cases and deaths, as well as key entomological and efficacy indicators, are required. Access to this information would allow for more useful interventions to be planned, since vulnerable areas or population groups could be identified and specifically targeted. Moreover, adequate responses to predicted malaria outbreaks could be anticipated and implemented more efficiently.

In order to understand whether malaria surveillance systems are fit for purpose, regular monitoring of their structure, core and support functions, as well as evaluation of the quality of the data is also strongly recommended by the WHO.

2.1. MALARIA LIFECYCLE

Malaria is caused by a protozoan parasite belonging to the genus Plasmodium. Although more than 100 species of Plasmodium have been identified, there are only five species that are known to infect humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi (CDC, 2018a).

Plasmodium falciparum is the most common cause of infection in Africa and South East Asia, being responsible for approximately 99.7% and 50% of all malaria cases, in each respective region (WHO, 2019).

The life cycle of malaria parasites involves two different species: female Anopheles mosquitoes (the vectors, whose bites are the mode of transmission of the parasite between human hosts) and humans (Figure 2.1).

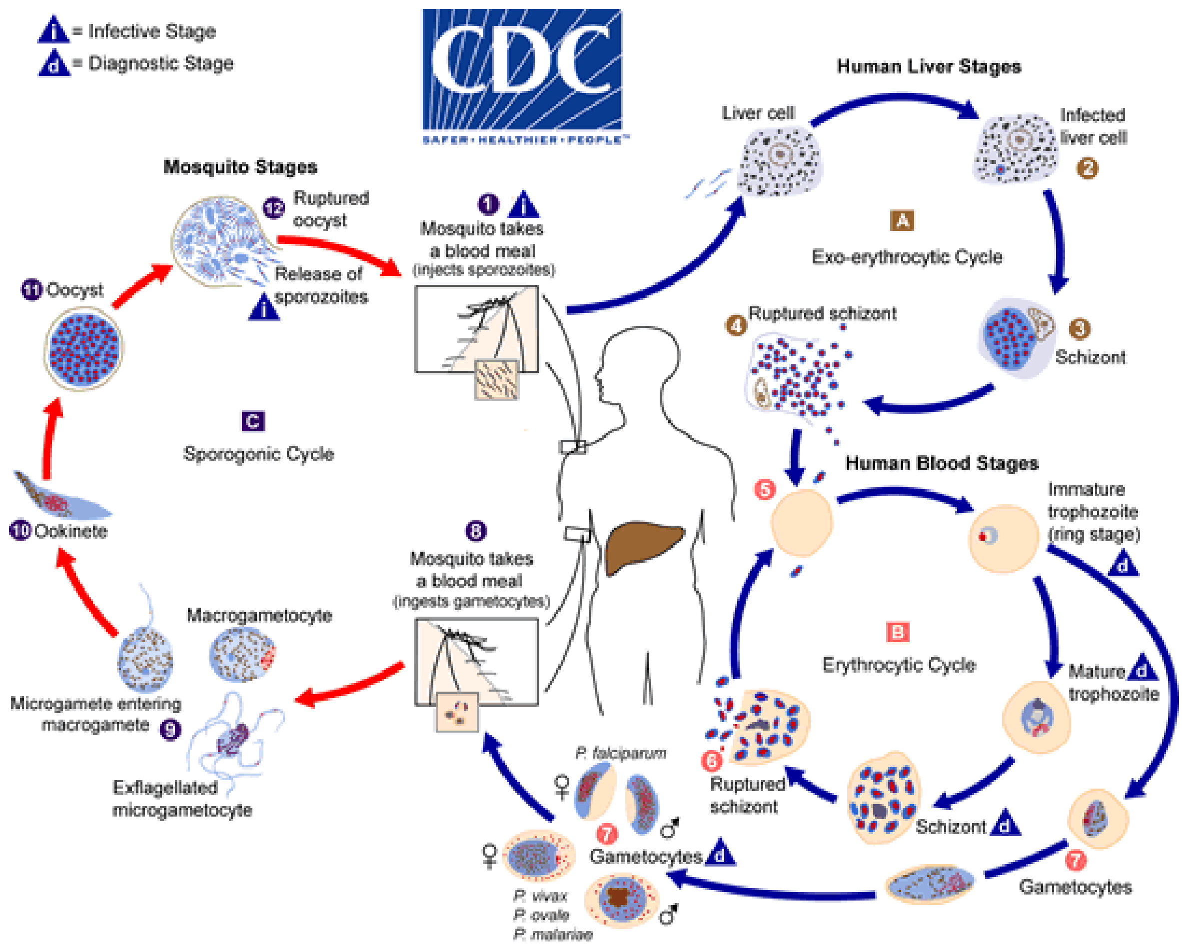

Figure 2.1 – Malaria life cycle (CDC, 2018b)

Infected mosquitoes carry Plasmodium parasites on their salivary glands, in the form of sporozoites. During a blood meal, the sporozoites are injected into human hosts, travelling through the bloodstream until reaching the liver. Inside hepatocytes, sporozoites undergo an asexual replication stage, known as exo-erythrocitic schizogony, during which they mature into schizonts and multiply to up to tens of thousands of merozoites. After a period ranging between 8 to 30 days, mature schizonts rupture, releasing merozoites back into the bloodstream, where they can invade red blood cells.

The erythrocitic schizogony stage is a period of asexual multiplication that occurs inside red blood cells, during which merozoites develops into trophozoites, which subsequently mature into schizonts. Each mature schizont contains around 20 merozoites that are released after rupturing the erythrocyte to invade further red blood cells. Each cycle takes around 48h to complete (72h for Plasmodium malariae). It is this synchronous lysis of erythrocytes that is responsible for the characteristic clinical manifestations of the disease.

A small proportion of the merozoites within red blood cells differentiate into male or female gametocytes (sexual erythrocytic stage), which have no further activity within the human host. Gametocytogenesis can take from 5 to 23 days, depending on the infecting species. These gametocytes are essential for transmitting the infection to other humans, as they can be ingested by female Anopheles mosquitoes during a blood meal.

The parasites' multiplication within the mosquito is known as the sporogonic cycle. Inside the mosquito's stomach, gametocytes generate zygotes, which in turn become motile ookinetes that invade the midgut wall where they develop into oocysts. Sporogony within each oocyst produces many sporozoites. When the oocyst ruptures, sporozoites are released and migrate to the salivary glands. The sporogonic cycle is completed after 10 to 18 days and thereafter the mosquito remains infective for 1 to 2 months. These infected mosquitoes inoculate the sporozoites into new human hosts, therefore perpetuating the malaria life cycle (CDC, 2018b; Tuteja, 2007).

This intricate life cycle is influenced by different biological characteristics from both the parasites and the mosquitoes that rely not only on several climatic and environmental factors, but also on complex ecological and social interactions between hosts, the migration of population between endemic and non-endemic areas as well as on the evolutionary pressure of drugs and control measures contributing to drug resistance of parasite (Mandal et al., 2011).

All of these aspects contribute to the continuously unsuccessful attempts to adequately model, predict or prevent malaria transmission, despite all of the global initiatives being undertaken.

2.2. THE INFLUENCE OF CLIMATE ON MALARIA TRANSMISSION

There is no doubt that climate plays an important role in the dynamics and distribution of malaria. Factors such as temperature, humidity and rainfall have a significant impact in mosquito development, reproduction and longevity and therefore impact the parasite's survival and capacity to infect human hosts (Mandal et al., 2011).

In a systematic review of 152 papers analysing the seasonality of malaria transmission, Reiner et al. (2015) found that temperature and precipitation have been identified as significant drivers of malaria considerably more than any other climatic variable.

The majority of those studies evaluated the relationship between malaria metrics and temperature (40%) or rainfall (34%). Vegetation coverage indices were investigated in 11% of cases, often in combination with the two former variables. All other potential features, such as humidity, wind speed and direction or sunspots were used rarely (2.5%) or in conjunction with other main drivers (13%).

2.2.1. Temperature effects

Temperature can significantly influence several of the mosquito and parasite features including mosquito development rate, biting rate, and development rate and survival of the parasite within the mosquito (Blanford et al., 2013).

Because changes in temperature affect multiple parts of the pathogen life cycle, this climatic variable holds the most complex relationship with malaria transmission and exerts a stronger influence on the rate of disease spread, as long as the remaining environmental conditions are also within an acceptable range (Parham & Michael, 2010).

When analysing temperature-based variables, researchers have almost always resorted to monthly data, uncovering significant relationships either with minimum, maximum or mean monthly temperatures. According to Reiner et al. (2015), minimum monthly temperature has been the most frequently found to be significantly related with malaria. Also, the range of significant time lags between monthly temperature and malaria metrics has considerably varied, extending from zero to nine months.

Parham and Michael (2010) found that the rate of malaria transmission is significantly increased at temperatures around 32–33°C, with the number of cases doubling every 1.5 to 2.5 months. Outside of this temperature range, the doubling time would strongly depend on mosquito density.

During the development of their weather-driven mathematical malaria model, which will be presented in section 2.3.1, Hoshen & Morse (2004) determined that in order to achieve effective parasite transmission to humans, mosquito maturation and survival requires average daily temperatures above 20°C and moderate rainfall (at least 10–20 mm/10 day period).

On the other hand, mean temperatures below 5°C (Craig, Le Sueur, & Snow, 1999) or above 40°C (Kirby & Lindsay, 2004) are incompatible with vector survival.

Oviposition, i.e., egg production from female mosquitoes only takes place when temperature rises above 10◦C. Furthermore, the speed of egg development is also strongly influenced by temperature conditions (Detinova, 1962). Li et al., (2002) determined that a temperature change from 12 to 31°C can significantly reduce the time required for mosquito breeding, decreasing from 65 to only 7 days.

According to Bayoh (2001), who investigated the development and survival of Anopheles gambiae mosquitoes at various temperatures and relative humidities, the vector's development rate increased linearly when temperatures rose from 18ºC up to an optimum temperature of 28°C. Although the rate of larval development was greatest between 28-32°C, the proportion of larvae that developed into adults was highest between 22-26°C. The lower limit for complete development to adult occurred at 16°C and the upper threshold was 34°C.

Regarding the sporogonic cycle of the parasite within mosquito vectors, while at 16°C it is completed after 55 days, that period reduces to 7 days at 28°C (Martens et al., 1995).

There is a greater uncertainty concerning the minimum temperature threshold that allows for sporogony to occur. While some authors refer that the parasite's development within the mosquito ceases below 18ºC (Bouma et al., 1994; Githeko el al., 2000; Hoshen & Morse, 2004; Patz & Lindsay, 1999; Patz & Reisen, 2001), others quote a value of 16°C or lower (Charlwood et al., 1997; Craig et al., 1999; Hay et al., 2000; Hay et al., 2004; Ikemoto & Takai, 2000; Kiszewski et al., 2004; Martens, WJ, 1998; Martens, 1999; Martens et al., 1999; Patz et al., 1996; Reiter, 2000; Sachs & Malaney, 2002; Snow et al., 1999).

The choice between these values can be particularly important when the temperatures from the regions being studied are closer to the threshold. However, it has been suggested that the data collected by weather stations is unlikely to match the conditions in the microhabitats where vectors spend most of their time (Hay et al., 1996; Kovats et al., 2001). By resting in more climatically stable and warmer houses, mosquitoes may avoid the restrictions caused by lower temperatures on the progress of parasite development (Epstein et al., 1998; Koenraadt et al., 2006; Reiter, 2001).

Interestingly, most studies analysing malaria–temperature relations are based solely on mean temperatures, although mosquitoes and parasites are exposed to temperatures that fluctuate throughout the day.

In light of that, some researchers have investigated how, in addition to mean temperatures, daily fluctuations in temperature can affect malaria transmission and found that several essential biological events (parasite infection, parasite growth and development, immature mosquito development and survival, length of the gonotrophic cycle and adult mosquito survival) are sensitive to daily variation in temperature. When compared with rates at equivalent constant mean temperatures, temperature fluctuation around lower temperatures acts to speed up processes, whereas fluctuation around higher temperatures slows the processes down (Blanford et al., 2013; Paaijmans et al., 2009; Paaijmans et al., 2010; Waite et al., 2019).

These findings suggest that, if mean temperatures alone are used to characterize potential malaria transmission, under cool conditions this approach will underestimate parasite development, while under warmer conditions development will be overestimated.

The potential impact of temperature fluctuations was also highlighted by Tanser et al. (2003), who analyzed malaria transmission profiles in regions with stable and seasonal malaria incidence. The authors determined that in stable malaria areas monthly mean temperatures showed little variation throughout the year, whereas in regions where malaria transmission follows a seasonal pattern, the average monthly temperatures display a stronger fluctuation.

2.2.1. Precipitation effects

Precipitation (or rainfall) is critical in providing stagnant water bodies, which are the most suitable habitats for mosquitoes to reproduce.

Despite being less predictable and more difficult to quantify in comparison to temperature, seasonal changes in rainfall patterns have been found to significantly alter mosquito density, therefore strongly impact malaria endemicity, invasion and extinction, even at optimal temperatures (Parham & Michael, 2010). In fact, given that the sustainability of the mosquito population depends on adequate precipitation, this variable seems to be a more important driver of malaria transmission in Africa than temperature (Morse et al., 2005). Conversely, when sufficient rainfall exists, then temperature exerts a stronger influence on the intensity of disease transmission (Parham & Michael, 2010).

At a regional level, local topography combined with precipitation will also influence the spread of malaria, since flat areas on the ground are more prone to accumulate water and therefore incur in an increased malaria risk (Chikodzi, 2013). Not surprisingly, the distance from water bodies has also been identified as a risk factor for increased malaria incidence (Ferrão et al., 2018; Krefis et al., 2011; Zhou et al., 2012).

Mosquitoes can deposit their eggs in ponds, puddles or even hoof prints (Fontenille et al., 1997). These open water surfaces are created after rainfall events and persist for approximately ten days (Shaman & Day, 2007). Consequently, mosquito density increases rapidly following the start of the rainy season (Lindsay & Birley, 1996; Omer & Cloudsley-Thompson, 1970) whereas during the dry season the number of available vectors for malaria transmission is much lower (MARA, 1998). Because the availability of adequate breeding sites strongly depends on seasonal precipitation, this is the reason why malaria is also mostly seasonal in Africa.

Nevertheless, in endemic areas, malaria incidence during dry seasons will continue due to the presence of slow-flowing rivers, lakes, swamps or other man-made surface water sites (Hay et al., 2000; Ijumba, Mosha, & Lindsay, 2002; Keiser, Utzinger, & Singer, 2002).

On the other hand, excessive rainfall can be detrimental to mosquito reproduction as it leads to the flushing of breeding habitats (Gimnig et al., 2001; Paaijmans et al., 2007; Shaman & Day, 2005), hence causing a paradoxical decrease in malaria transmission (Drakeley et al., 2005).

Consequently, it has been demonstrated that the availability of suitable mosquito habitats is not a simple linear function of rainfall (Shaman & Day, 2005). Probably due to this non-linear association, although mean monthly rainfall has been the most frequent metric to be investigated in relation to malaria (Reiner et al., 2015), other variables have also been employed, such as seasonal rainfall (Mabaso et al., 2007) or total rainfall during a fixed period (Small, Goetz, & Hay, 2003). Time lags found to be statistically significant varied between zero to six months (Reiner et al., 2015).

Other factors that can influence the aquatic stage of mosquito development include water quality, food supply, overcrowding, cannibalism, as well as the existence of predators, parasites or other pathogens (Bayoh & Lindsay, 2004; Koenraadt & Takken, 2003; Munga et al., 2006; Paaijmans et al., 2007; Service, 1973).

2.2.1. Humidity effects

Mosquitoes, like all insects, have a limited range of tolerable temperature and humidity. Their tracheal system of respiration, small size and large surface area makes them especially sensitive to desiccation at low humidity levels. As such, the ideal conditions for most vector species are met when relative humidity is greater than 60%. Conversely, at relative humidity levels under 10%, mosquitoes cannot survive more than a few hours (Fouet et al., 2012; Gray & Bradley, 2005).

Desiccation stress and subsequent mosquito longevity decrease has been showed to begin when relative humidity falls below 40% (Bayoh, 2001; Liu et al., 2011; Wang et al., 2011). However, in the range between 10-40% there is very little information regarding the effect of humidity on mosquito survival (Yamana & Eltahir, 2013).

In contrast, a highly saturated environment may lead to a reduction on mosquito survival due to drowning (Bayoh, 2001)

As Bayoh (2001) pointed out, it is very difficult to separate the influence of humidity from that of temperature on mosquito longevity. However, there does not seem to be a direct relationship between survival and relative humidity.

2.3. MATHEMATICAL MODELS OF MALARIA

One of the earliest mathematical models that explored the relationship between the number of mosquitoes and incidence of malaria in humans, now known as the Ross model, was published in the early 1900 by Sir Ronald Ross (Ross, 1911). In his model, Ross divided both the human and the mosquito population into susceptible and infected compartments, and used two differential equations to study the time evolution of the fraction of individuals in their respective infected classes.

By placing the main burden of malaria transmission on mosquito-specific features, the Ross model already enlightens the importance of mosquito eradication as a strategy to control malaria outbreaks.

More than 40 years later, George Macdonald (1957) enhanced Ross's model by including other factors, such as the latency period required for parasite development within mosquitos (referred to as the "exposed mosquitoes" class) during which there is no effective malaria transmission, and estimations for the proportion of bites which are infective. With his work, Macdonald reinforced the role of mosquito longevity as the single most important factor responsible for the spread of malaria.

The concept of latency of infection in humans was introduced by Aron & May (1982) who further developed Macdonald's model by including the exposed human compartment.

The Garki model (Dietz, Molineaux, & Thomas, 1974) accounted for acquisition, maintenance and loss of immunity in humans, as well as the presence of superinfection. It was subsequently modified for areas of unstable malaria transmission (Struchiner, Halloran, & Spielman, 1989).

According to Mandal et al. (2011), who published a review of mathematical models of malaria in 2011, the Ross, Macdonald and Aron-May models are the pivotal basis from which most subsequent models developed from. In an attempt to obtain a more realistic and precise representation of the disease, researchers have progressively increased the complexity of interactions between additional factors, such as age-related differential susceptibility to malaria (Anderson & May, 1991; Aron & May, 1982; Dietz, 1988), acquired human immunity (Aron & May, 1982; Aron, 1988; Filipe et al., 2007), spatial and genetic diversity among parasites and hosts (Gupta & Hill, 1995; Gupta, Swinton, & Anderson, 1994; Hasibeder & Dye, 1988; Rodríguez & Torres-Sorando, 2001; Torres-Sorando & Rodríguez, 1997).

The social and economic conditions of the population also appear to be intimately related to malaria risk. Several authors have investigated and identified socioeconomic indicators such as poverty level, population growth, premature mortality or misdiagnosis to be correlated with malaria incidence (Amexo et al., 2004; Laxminarayan, 2004; Martens et al., 1999; Sachs & Malaney, 2002; van Lieshout et al., 2004; Wyse et al., 2007). These conditions may not only be independently related with malaria risk, but can also modulate the magnitude and direction of associations between climate and malaria (Manh et al., 2011).

In 2013, Tusting et al. conducted a systematic review and meta-analysis to assess whether the risk of malaria in children under the age of 15 years was associated with socioeconomic status and concluded that the odds of malaria infection were higher among the poorest children. The authors went on to recommend the need for interventions to support socioeconomic development, since such actions could prove highly effective and sustainable against malaria in the long term.

Furthermore, in areas where malaria is endemic, changes in social and economic conditions were considered to be of greater impact on malaria transmission than climate change (Yang & Ferreira, 2000).

Another important aspect that should be taken into account when predicting the incidence of malaria is the mobility of human hosts. Human migration and visitation can enhance malaria incidence and transmission not only in endemic region but also in areas where the disease has already been eradicated, therefore contributing to the spatiotemporal persistence of this disease (Aragón, 1992; Martens & Hall, 2000; Martens, P, 1998; Sandia-Mago, 1994; Torres-Sorando & Rodríguez, 1997).

Additionally, the impact of human activities such as the modification of the landscape by irrigation (Briët, 2002), forest clearing (Munga et al., 2006) or urbanization (Hay et al., 2005; Keiser et al., 2004) have also been found to significantly alter malaria transmission.

2.3.1. Weather-driven malaria models

Between 1997 and 1998, the El Nino phenomenon caused many anomalous weather conditions in different parts of the globe, including prolonged torrential rains over East Africa (Stockdale et al., 1998) which were later associated with a major malaria outbreak in north-eastern Kenya (Brown et al., 1998).

Following this event, the scientific community showed an increasing interest in the use of weather forecasts for predicting malaria epidemics and setting up early warning systems (Githeko & Ndegwa, 2001; WHO, 2001).

Moreover, with growing awareness about globate warming, many researchers have dedicated their efforts into predicting how climate change will modify the worldwide distribution of malaria, with conflicting results.

For example, Craig et al. (1999) developed a fuzzy-logic model based on mean temperature and rainfall that could be used to represent the impact of these variables on malaria transmission. This model indicated that an annual average temperature of 22ºC is sufficient for perennial malaria transmission and the approximate temperature cut-off point between epidemic and no-malaria regions is around 18°C. As for precipitation, a minimum rainfall of 80 mm per month for at least five months would be required in order to achieve stable malaria transmission. At that time, the authors suggested that this could be used as a baseline against which climate change scenarios could be evaluated in the long term.

Martens et al. (1995) applied a rules-based modelling approach to predict the implications of different climate chance scenarios on malaria transmission at a global level. Their estimations pointed to a widespread increase of malaria risk, particularly at the borders of malarial areas, where mosquitoes already existed but the development of the parasite was currently refrained by temperature, and also at higher altitudes within malarial areas.

Peterson (2009) estimated the future potential for human exposure to malaria across Africa over a 50 year period, integrating different climate change scenarios and spatial summaries of population distributions. Using ecological niche models projections, the model predicted an overall reduction in the number of people at risk. However, although malaria vector suitability was likely to decrease in West Africa, it would increase in eastern and southern Africa, resulting in novel public health problems in areas where it has not previously been common.

Rogers & Randolph (2000) used a statistical model applied to future global circulation models scenarios to predict the potential impact of global warming on malaria distribution. They determined that even under the most extreme scenarios, the geographical distribution of malaria would be very similar to what occurs today.

However, other than geographical expansion, the changing climate can also influence the seasonality of malaria and result in longer periods of exposure to the disease, if favorable environmental conditions for both vector and parasite development persist.

The potential effect of projected climate scenarios on malaria transmission patterns was analyzed by Tanser et al. (2003), whose model estimated a potential increase of 16–28% in person-months of exposure by the year 2100, across all scenarios. This effect was even more pronounced in areas of existing transmission (28–42% of new person-months of exposure) due to the increase in the length of transmission season in these regions.

On the other hand, Hay et al. (2002) analysed long-term trends in meteorological data in the East African highlands using a 95-year data set and a regression approach. Their work showed that temperature, rainfall, vapour pressure and the number of months suitable for malaria transmission had not changed significantly during the past century neither during the period of reported malaria resurgence. Hence, the authors concluded that changes other than climate should have been responsible for the observed increases in malaria incidence.

Similar findings were published by Gething et al. (2010), who compared historical and contemporary maps of malaria distribution, documenting a marked global decrease in the geographic extent and intensity of malaria transmission during the last century, despite the unequivocal increase in global temperature. Given the known biological effects of temperature on malaria epidemiology, that have been previously addressed in chapter 2.2.1, the authors assumed that non-climatic factors must have exerted a substantially greater influence on the worldwide distribution of malaria rather than climatic factors.

Although this line of research has undoubtedly resulted in a much more comprehensive understanding of the relationships between climate and malaria (particularly concerning the effects of temperature, precipitation and, in a smaller extent, humidity), these models are not able to predict short-term variations on malaria risk, either within or between seasons.

With this in mind, Hoshen & Morse (2004) designed a weather-driven mathematical biological model of malaria parasite dynamics, known as the Liverpool Malaria Model (LMM), which combines climate-dependent within-vector stages as well as climate-independent within-host stages. The LMM simulates the daily spread of malaria, using mean temperature and 10-day accumulated precipitation. This model can not only be used for assessing the impact of climate change on malaria transmission (Ermert, 2009) but also for seasonal forecasting of the disease's progression (Jones, 2007; Jones & Morse, 2010).

Hence, Ermert (2009) applied the LMM to assess the occurrence of malaria in Africa under the influence of observed and projected climate change using regionalized climate projections. Underlining the importance of temperature and rainfall on malaria transmission dynamics, the results pointed to a significant decrease of malaria transmission in sub-Saharan Africa due to the predicted precipitation decline. However, significantly higher temperatures and higher rainfall will lead to a substantial enhance in the season length and parasite prevalence in parts of East Africa. As a result, malaria transmission will be markedly augmented in this region.

Later, Ermert et al. (2011a) developed a new version of the LMM, reassessing the parameter settings by means of a comprehensive literature survey, as well as performing an extensive validation and calibration of their new LMM against meteorological data and malaria observations from West Africa (Ermert et al., 2011b). Unlike the original model, which could only be applied to epidemic malaria regions, the revised LMM's usage was also extended to endemic areas.

2.4. THE IMPACT OF MALARIA IN MOZAMBIQUE

Malaria poses a serious threat to public health in Mozambique, as it is considered one of the most deadly diseases in the country. According to the WHO, there have been almost 9 million reported cases of malaria in 2017, which means that this disease affected at least 30% of the country’s population (WHO, 2018). The majority of cases are caused by Plasmodium falciparum.

Malaria is responsible for 44% of all outpatient consultations and 65% of pediatric hospital admissions. It is also the leading cause of death among hospitalized children in Mozambique (Zacarias & Andersson, 2010).

Globally, the country's favorable climatic conditions allow for sustained development and transmission of malaria, although some drier parts of the country are epidemic-prone. Therefore, malaria is considered to be endemic to Mozambique, which means that transmission takes place all year round. There is, however, a known seasonal peak that extends from December to April (Zacarias & Andersson, 2010). As previously explained, the seasonality of malaria is Mozambique is closely related to the duration of the rainy season, which takes place between November and March.

Zacarias and Andersson (2011) analyzed spatial and temporal patterns of malaria incidence in southern Mozambique, establishing that several climatic features (temperature, rainfall and humidity) were determinant for malaria transmission and intensity in the region.

Socioeconomic status can also influence malaria risk in Mozambique, as higher levels of education and income have been identified as being protective against malaria. The prevalence of malaria is also lower in urban versus rural areas (INE, 2013b).

2.4.1. Malaria in Chimoio

Chimoio is a municipality located in the Manica Province, a region located in central Mozambique. It is the country's fifth-largest city, with an estimated population of 285 716 inhabitants (INE, 2013a)

Contrary to the decreasing trend in Africa, annual malaria cases have been increasing in Chimoio since 2010. In 2014, approximately 27% of the population was diagnosed with malaria. In the same period, the average malaria incidence in the WHO African region was 24.6% (WHO, 2015b). It has been suggested that this increase could be explained by the annual increase in population, aggravated by persistent poverty and reduced efforts dedicated to combat malaria (Ferrão et al., 2016).

The disease affects both males and females equally. However, children under 5 years of age are three times more prone to be infected, probably due to their lack of acquired immunity against the parasite (Ferrão et al., 2016).

The highest number of cases occurs in February (peak of the rainy season) and the lowest is seen in September, during the dry season. Correspondingly, malaria mortality rates are significantly higher in January, February and March, when compared to the remaining months of the year. The seasonality of malaria incidence and mortality in Chimoio has previously been associated with the amount of rainfall that occurs six to eight weeks before (Ferrão et al., 2017a; Ferrão et al., 2017b).

The same authors found that mean temperature was also a significant predictor for malaria occurrence. Additionally, when weekly minimum temperature remained below 18ºC, an accentuated reduction in malaria cases was observed.

Relative humidity in Chimoio rests consistently above the optimal threshold for mosquito survival. As such, this variable does not seem to restrict malaria incidence in Chimoio (Ferrão et al., 2017a).

3. METHODOLOGY

To evaluate the association between malaria transmission and environmental variables, a wide variety of statistical approaches have been applied, ranging from simple descriptive analysis and purely correlative approaches to complex spatio-temporal methods.

According to Ebhuoma and Gebreslasie (2016) and Reiner et al. (2015), the most frequently employed methods of statistical analysis in this line of research have been regression models, particularly linear, logistic and Poisson regression. In addition, several multivariate methods and mixed models were also commonly used.

An overview of publications investigating malaria disease and its relation with numerous environmental/climatic variables, where these statistical methods have been applied, can be found in Table 9.1 (Appendix 9.1).

For the purpose of this study, we intend to apply time series analysis and regression modelling, by resorting to a generalized additive model (GAM) methodology in order to further explore the relationship between malaria incidence and selected climatic variables.

3.1. STUDY AREA

Chimoio is a municipality located in the Manica Province, in the central region of Mozambique (Figure 3.1). Chimoio comprises an area of 174 km^2 at an altitude of 750 m. In 2013, the population was 285 716 inhabitants (INE, 2013a).

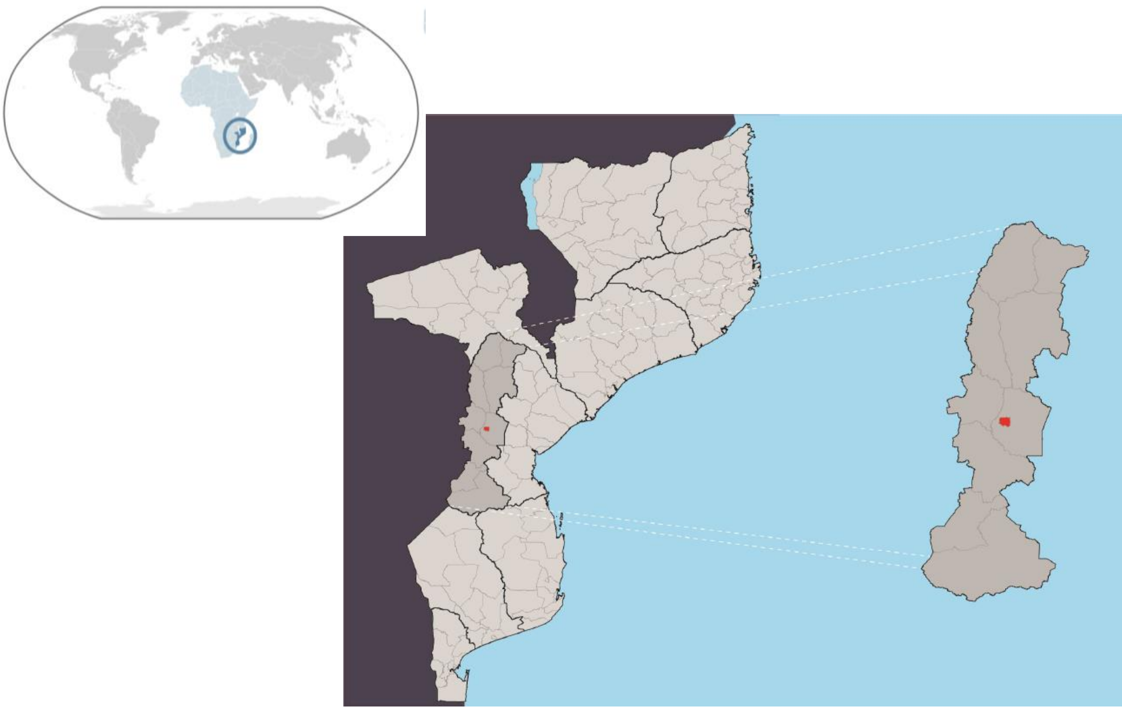

Figure 3.1 – Map of Chimoio (INE, 2013a)

This region presents a warm temperate climate with dry winters lasting between April to July, hot and dry summers from August to October, and hot humid summers from November to March (Ferrão et al., 2016).

The mean annual temperature is 22.3°C, the mean relative humidity 67.4% and the average annual precipitation is 946 mm (INE, 2013a). The average annual number of dry days surpasses wet days, with the latter being restricted to the rainy season, between November and March (Westerink, 1995).

3.2. DATA DESCRIPTION

A previously compiled database was provided (Ferrão et al., 2017a) containing weekly data from the Chimoio district, collected during a nine-year period (2006 to 2014).

The available variables were:

- number of reported malaria cases (Mal);
- maximum temperature (TMax);
- minimum temperature (Tmin);
- mean temperature (Tmean) [°C];
- relative humidity (RH) [%];
- precipitation (P) [mm].

3.2.1. Weekly malaria cases

The weekly number of reported malaria cases is represented in Figure 3.2. A simple visual inspection of the data reveals the known seasonality of malaria transmission, which is endemic to Mozambique (i.e., takes place all year round) with a seasonal peak that extends from December to April, slightly lagging after the onset and termination of the rainy season (Zacarias & Andersson, 2011).

Also, there was an isolated rise in the number of malaria cases between late 2007 and the beginning of 2008, for reasons that do not seem to be related to weather conditions. In the following years, a slower but steady growth in the number of cases has been observed. Table 3.1 – further depicts the yearly statistics associated with malaria cases.

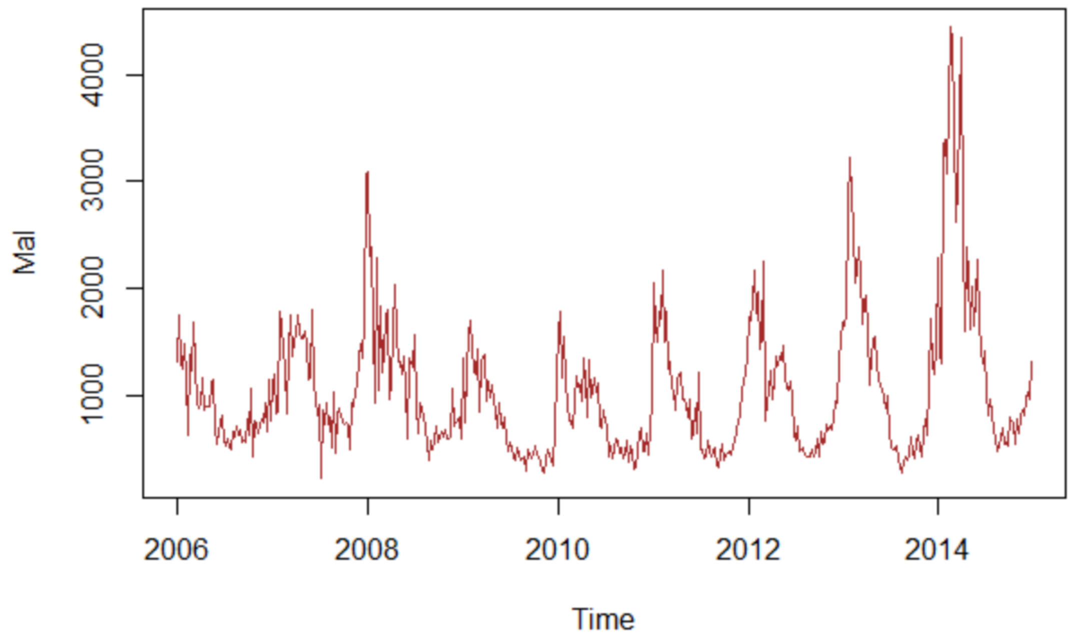

Figure 3.2 – Weekly malaria cases in Chimoio from 2006 to 2014

Table 3.1 – Characteristics of weekly malaria cases in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Mean	874	1160	1122	767	806	906	1009	1161	1629	1048
Standard Deviation	316,6	477,4	584,3	397,5	349,4	477,4	498,2	715,4	1126,6	642,1
Median	764	1101	951	643	726	803	951	1073	1300	884
Range	1314	2838	2689	1420	1466	1838	1832	2936	3949	4216
Minimum	438	222	397	276	317	332	425	281	489	222
Maximum	1751	3059	3086	1697	1783	2170	2257	3217	4438	4438
Sum	45458	60306	58333	39874	41925	47107	52463	60381	84707	490555

3.2.2. Temperature

Weekly minimum, maximum and mean temperatures in Chimoio between 2006 and 2014 are represented in Figure 3.3 to Figure 3.5 and Table 3.2 to Table 3.4. Other than the expected seasonal fluctuations, there do not appear to be significant differences in temperatures registered in Chimoio throughout the 9 recorded years.

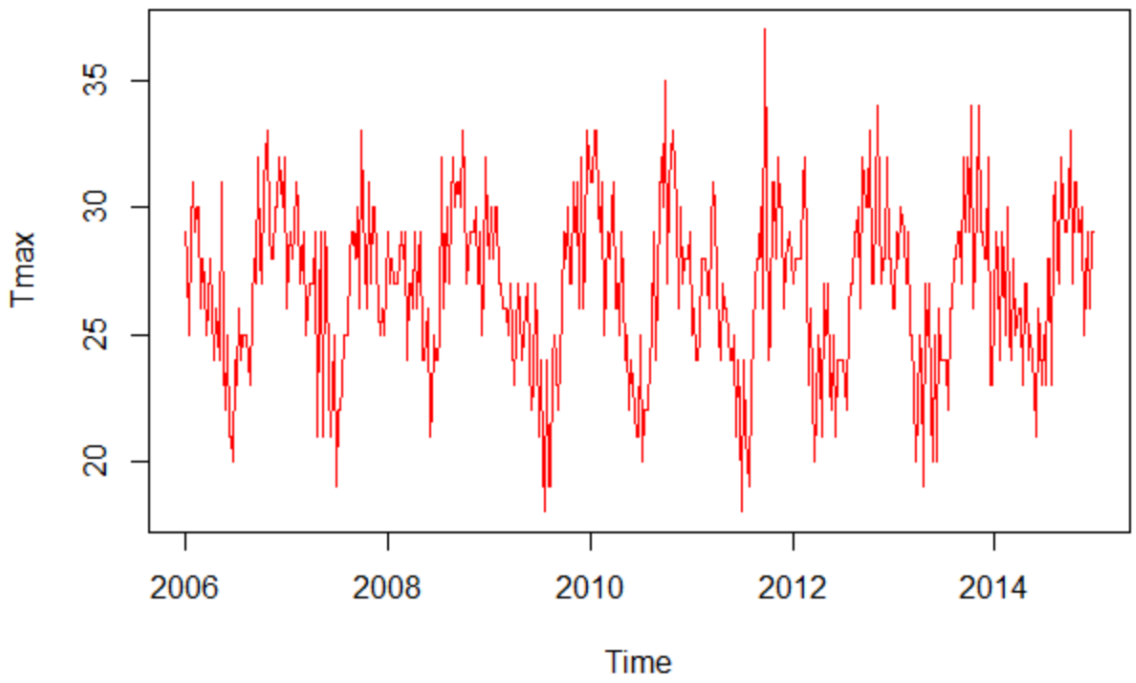

Figure 3.3 – Weekly maximum temperatures in Chimoio from 2006 to 2014

Table 3.2 – Characteristics of weekly maximum temperatures in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Mean	27	27	28	26	27	26	27	26	27	27
Standard Deviation	3,2	2,9	2,7	3,4	3,6	3,5	3,3	3,4	2,6	3,2
Median	27	27	28	26	28	26	27	26	27	27
Range	13	14	12	15	15	19	14	15	12	19
Minimum	20	19	21	18	20	18	20	19	21	18
Maximum	33	33	33	33	35	37	34	34	33	37

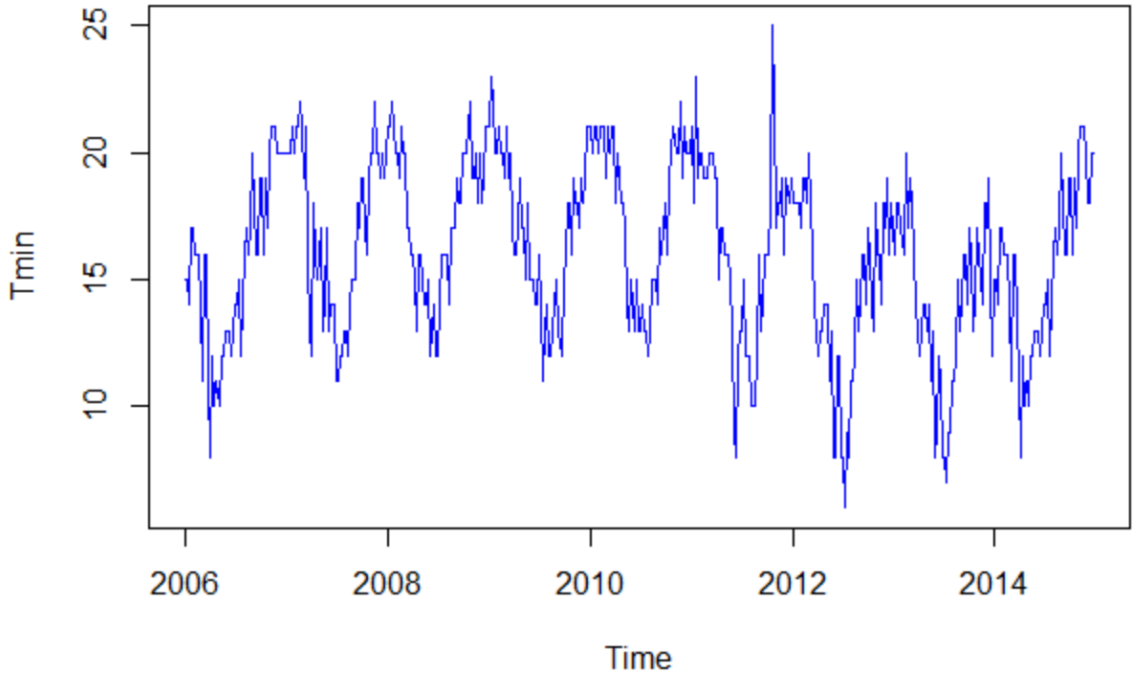

Figure 3.4 – Weekly minimum temperatures in Chimoio from 2006 to 2014

Table 3.3 – Characteristics of weekly minimum temperatures in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Mean	16	17	18	17	18	16	14	14	15	16
Standard Deviation	3,3	3,3	2,8	3,0	3,1	3,8	3,5	3,3	3,2	3,6
Median	16	17	18	17	18	16	14	14	16	16
Range	13	11	10	12	10	17	13	14	13	23
Minimum	8	11	12	11	12	8	6	7	8	6
Maximum	21	22	22	23	22	25	20	20	21	29

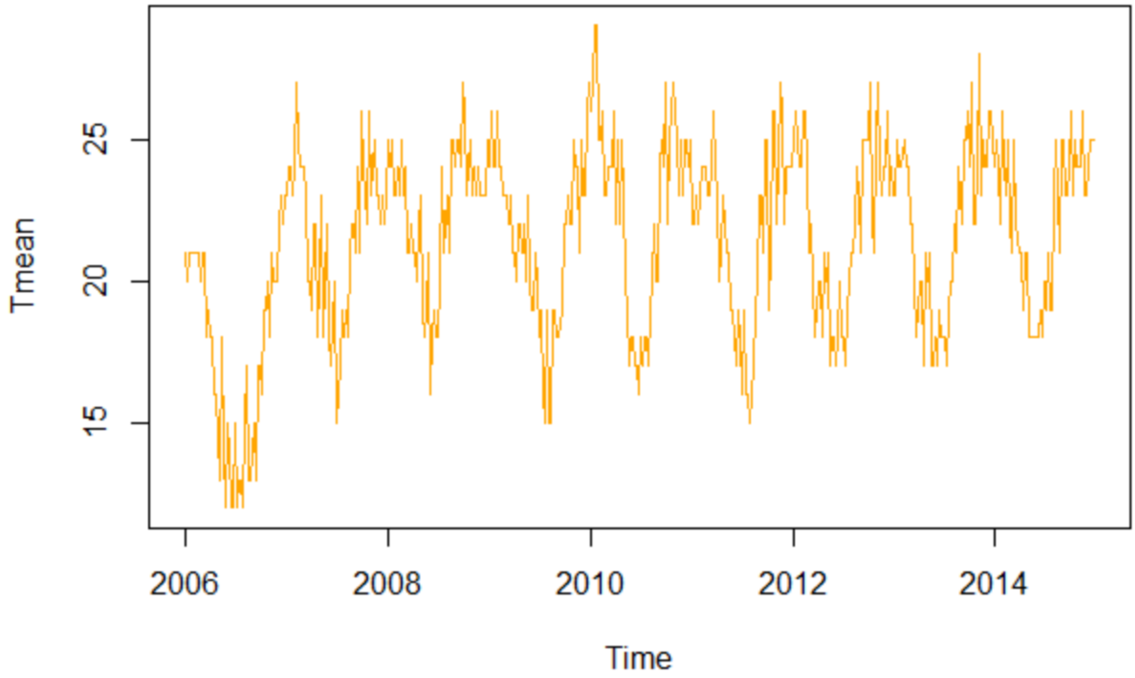

Figure 3.5 – Weekly mean temperatures in Chimoio from 2006 to 2014

Table 3.4 – Characteristics of weekly mean temperatures in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Mean	17	22	22	22	23	22	22	22	22	21
Standard Deviation	3,4	2,7	2,4	2,9	3,4	3,1	3,0	3,0	2,6	3,3
Median	18	22	23	22	23	22	22	22	23	22
Range	11	12	11	12	13	12	10	11	9	17
Minimum	12	15	16	15	16	15	17	17	18	12
Maximum	23	27	27	27	29	27	27	28	26	29

3.2.3. Relative humidity

Similarly to temperature, relative humidity in Chimoio seems to present an analogous seasonal variation, which has remained relatively stable between 2006 and 2014 (Figure 3.6 and Table 3.5).

In accordance to what is expected in a tropical climate, relative humidity remains considerably elevated throughout the year, rarely falling below 50% and with average values consistently around 70%.

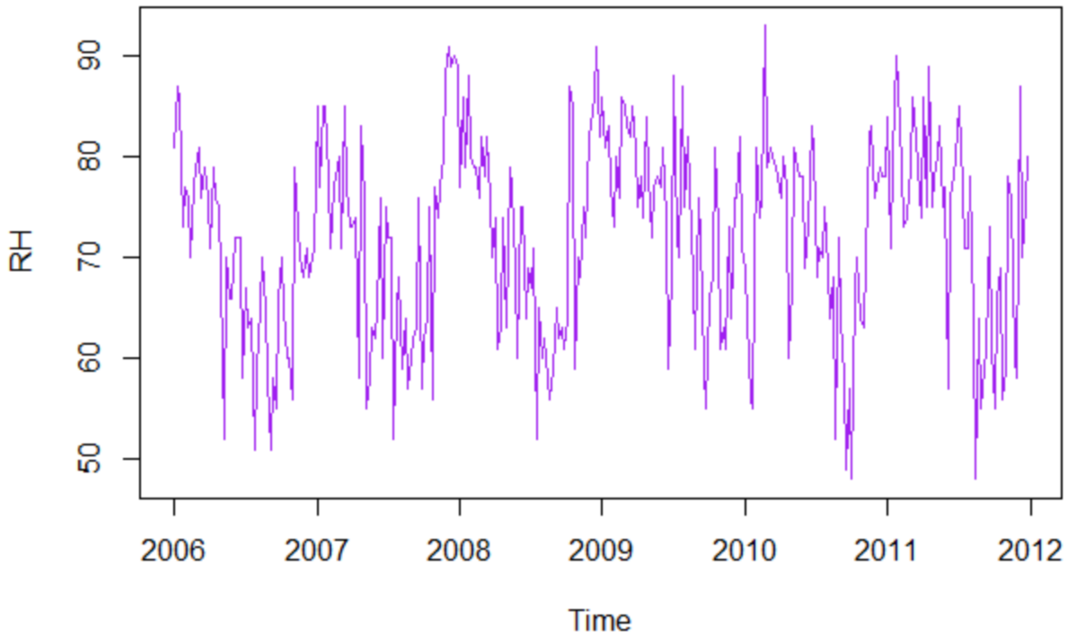

Figure 3.6 – Weekly relative humidity in Chimoio from 2006 to 2014

Table 3.5 – Characteristics of weekly relative humidity in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Mean	69	72	72	75	72	73	70	71	72
Standard Deviation	8,6	10,5	9,7	8,1	9,6	10,2	9,9	11,4	10,3
Median	70	74	73	76	74	75	73	73	71
Range	36	39	39	33	45	42	38	43	42
Minimum	51	52	52	55	48	48	51	48	54
Maximum	87	91	91	88	93	90	89	91	96

3.2.4. Precipitation

As mentioned, Chimoio usually presents a dry climate from April to October and a rainy season that lasts between November and March.

Accordingly, although average weekly precipitation is considerably low in Chimoio, the range and variability of these values are very high, which means that the number of rainy weeks is small, but the amount of rainfall occurring in this period can be quite elevated (Figure 3.7 and Table 3.6).

During the study period, there were three years in which precipitation was considerably higher: 2009, 2010 and 2013. In the remaining years, rainfall remained relatively constant.

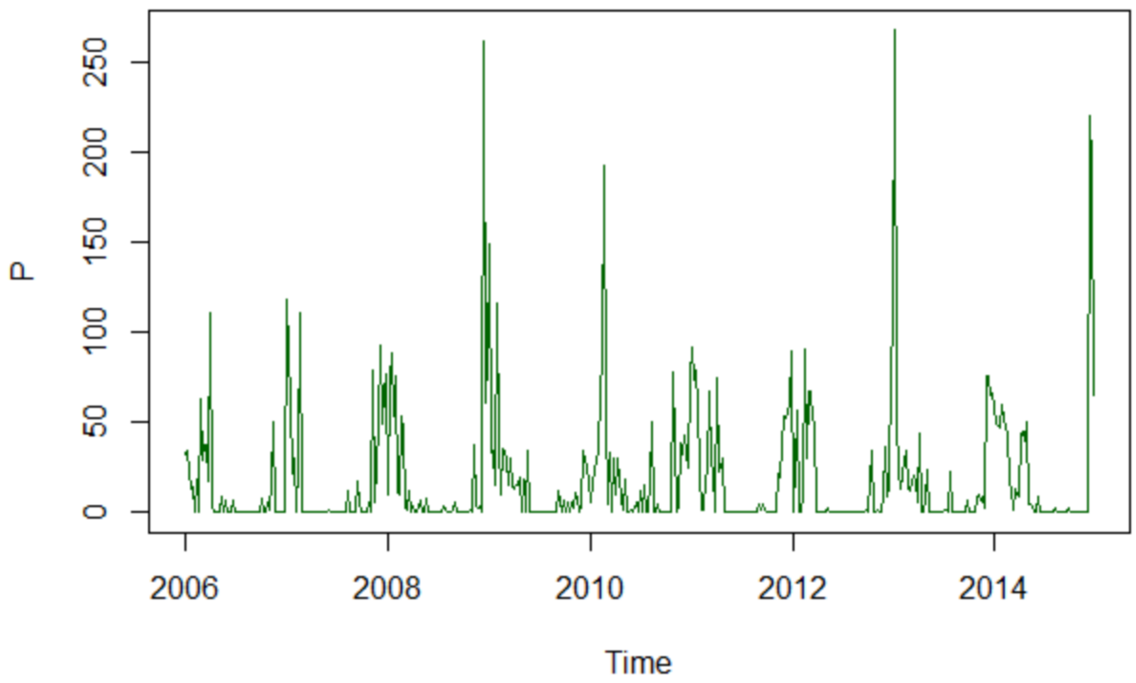

Figure 3.7 – Weekly precipitation in Chimoio from 2006 to 2014

Table 3.6 – Characteristics of weekly precipitation in Chimoio from 2006 to 2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Mean	11	18	18	16	21	19	13	20	22
Standard Deviation	20,4	32,6	42,4	26,9	33,1	27,8	23,9	42,4	43,1
Median	0	0	2	8	7	2	0	5	2
Range	111	119	262	149	193	92	91	268	220
Minimum	0	0	0	0	0	0	0	0	0
Maximum	111	119	262	149	193	92	91	268	220

3.3. GENERALIZED ADDITIVE MODELS

Linear models are statistical models in which a univariate response is modeled as the sum of a 'linear predictor' and a zero mean random error term. The linear predictor depends on predictor variables, measured with the response variable, and some unknown parameters, which must be estimated. Statistical inference is usually based on the assumption that the response variable is normally distributed.

Generalized linear models (GLM) surpass both the strict linearity premise of linear models as well as the assumption that the response is normally distributed, by allowing the expected value of the response to depend on a smooth monotonic function of the linear predictor and permitting it to follow any distribution from the exponential family.

A GAM is a GLM in which the linear predictor depends linearly on smooth functions of predictor variables. The degree of smoothness of the functions must be made controllable, so that models with varying degrees of smoothness can be explored. The selection of the most appropriate degree of smoothness is based on marginal likelihood maximization, cross validation, Akaike's Information Criteria (AIC) or Mallows' statistic (Wood, 2017).

In this case, a GAM was applied to the available data, in order to obtain the best possible explanatory model for the relationship between malaria incidence and selected climatic variables: TMax, Tmin, Tmean, RH and P.

The statistical analysis was performed using the mgcv package version 1.8-28 in Rstudio®.

Given the aforementioned scientific debate regarding the influence of temperature fluctuation rather than average temperatures on malaria transmission, we decided to experiment with the available temperature data separately, in an attempt to determine which of these metrics (TMax, Tmin or Tmean) would generate the best fitted model.

An additional variable, Mal_1, representing the number of malaria cases observed in the previous week (lag = -1) was also introduced, to serve as a reference point from which the malaria incidence in the current week can be determined.

Furthermore, it was also necessary to determine the appropriate time-frame between the observed local climate and its reflection on the occurrence of malaria. According to the available data gathered from the literature, the majority of studies found significant lag times ranging from 0 to 2 months for both temperature and rainfall, although some authors also suggested lag times as long as 4 months before achieving a significant effect between rainfall and malaria incidence.

Therefore, for the purpose of this study, we decided to analyze a possible lag interval ranging between 0 and 16 weeks (which corresponds to approximately 4 months). To find the optimal lag-time, an iterative step was added, in which the GAM was ran, using every possible lag-time combination for each climatic variable.

Also, in order to evaluate if the combination of different variables resulted in an effective increase in the model's performance, the GAM model was ran with every possible variable combination.

The selection of the optimal lag-time for each variable/ variable combination was based on the results from the AIC and Bayesian Information Criteria (BIC).

The models were formulated according to the following expression:

$$Mal = Mal\_1 + s(x_1 - h_1) + s(x_2 - h_2) + s(x_3 - h_3) + s(x_n - h_n)$$

Where Mal is the predicted number of weekly malaria cases for a given week, Mal_1 is the observed number of weekly malaria cases in the previous week, s() represents the smoothing function applied to each predictor variable, x_1 to x_n, and h_1 to h_n represents the lag-time (in weeks) applied to each predictor.

The dataset was divided into 2 subsets, for testing and validation purposes, respectively. Hence, the models were tested using the data from the first six available years (2006 to 2011), while the remaining three years of data (from 2012 to 2014) were used for the validation step.

To perform the validation process, an "out-of-sample" forecast approach was used, meaning that after each data point was predicted, the observed result was added to the test data and used to recalibrate the model before calculating the following prediction.

4. RESULTS

As explained, in order to characterize the relations between malaria incidence and climatic variables we chose to employ a statistical approach based on a GAM methodology, testing every possible variable combination to find the model that would yield the most accurate predictions.

In the first part of the analysis, each variable combination was tested, in order to determine the optimal lag-time (between 0 to 16 weeks) after which changes in that variable would most significantly influence weekly malaria incidence.

Table 4.1 displays the lag times for each variable/variable combination that resulted in the lowest AIC and BIC values.

Table 4.1 – Selected lag times for each variable/variable combination

Predictor variable	**Lag (weeks)**			
	One variable	**Temperature + RH**	**Temperature + P**	**Three variables**
Tmax	8	8	15	15
Tmin	8	7	8	12
Tmean	12	12	12	12
	One variable	**Temperature + RH**	**RH + P**	**Three variables**
RH	4	4, 10	2	12
	One variable	**Temperature + RH**	**RH + P**	**Three variables**
P	3	3	3	3

P: precipitation; RH: relative humidity; Tmax: maximum temperature; Tmean: mean temperature; Tmin: minimum temperature

It is interesting to note that when the weekly mean temperature and rainfall were used, the lag-time that produced the best results for each variable was the same for every combination: 12 weeks for mean temperature and 3 weeks for precipitation.

All other variables presented two or more distinct lag-times for different combinations. Relative humidity displays the most unpredictable behavior, with five different lag-times being selected in separate variable combinations.

Table 4.2 summarizes the results (adjusted R^2 and mean errors) obtained for each variable and variable combination, applying the lag times for which the AIC and BIC results were the lowest.

Using only one climatic variable to predict the weekly evolution of malaria incidence we are able to explain up to 65% of the variation in malaria cases, when the predictor is precipitation in the 3rd previous week. The lowest result was obtained using relative humidity lagged at 4 weeks. Among the possible temperature metrics, the results were very similar between themselves.

Models using two climatic variables as predictors, result in an improvement in the adjusted R^2, ranging from 1.3% to 13.2%. Although the highest increase occurred when combining mean temperature with relative humidity, the behavior of the remaining variables did not benefit significantly when combined with relative humidity. On the other hand, combining rainfall and temperature resulted in an adjusted R^2 increase from 9.3% to 12.3%, which was the highest overall increase for any combination.

The best results among this subset of models were achieved using a combination of maximum temperature lagged at 15 weeks and precipitation in the 3rd previous week.

Table 4.2 – Summarized results for each variable/variable combination applying the selected lag times

Model	adjR^2 (%)	MAE	RMSE	MAPE (%)
One climatic variable				
I. Mal = Mal_1 + s(Tmax-8)***	60.4	368.33	687.65	35.1
II. Mal = Mal_1 + s(Tmin-8)***	59.8	322.65	548.94	30.8
III. Mal = Mal_1 + s(Tmean-12)***	59	308.78	544.59	29.5
IV. Mal = Mal_1 + s(RH-4)***	56.3	336.03	602.67	32.1
V. Mal = Mal_1 + s(P-3)***	65.3	364.12	653.20	34.7
Two climatic variables				
VI. Mal = Mal_1 + s(Tmax-8)*** + s(RH-4)***	63.5	345.69	623.54	33.0
VII. Mal = Mal_1 + s(Tmin-7)*** + s(RH-4)***	61.9	315.01	557.94	30.1
VIII. Mal = Mal_1 + s(Tmean-12)*** + s(RH-10)***	72.2	323.97	598.35	30.9
IX. Mal = Mal_1 + s(Tmax-15)*** + s(P-3)***	72.7	319.85	566.03	30.5
X. Mal = Mal_1 + s(Tmin-8)*** + s(P-3)***	69.1	337.73	573.46	32.2
XI. Mal = Mal_1 + s(Tmean-12)*** + s(P-3)***	70.3	323.12	563.62	30.8
XII. Mal = Mal_1 + s(RH-2)*** + s(P-3)***	66.6	346.64	636.71	33.1
Three climatic variables				
XIII. Mal = Mal_1 + s(Tmax-15)*** + s(RH-12)*** + s(P-3)***	72.9	320,45	555,33	30.6
XIV. Mal = Mal_1 + s(Tmin-12)*** + s(RH-12)*** + s(P-3)***	71.7	321,16	579,04	30.6
XV. Mal = Mal_1 + s(Tmean-12)*** + s(RH-12)*** + s(P-3)***	71.9	320,90	555,60	30.6

adj: adjusted; MAE: mean absolute error; MAPE: mean absolute percentage error; P: precipitation; RH: relative humidity; RMSE: root mean square error; Tmax: maximum temperature; Tmean: mean temperature; Tmin: minimum temperature

*** $p < 0.001$

Interestingly, the outcome of combining three climatic variables did not improve significantly when compared to the models using two predictor variables, with the possible exception of minimum temperature, where the adjusted R^2 increased from 69.1% (Tmin+P) to 71.7% (Tmin+RH+P).

Nevertheless, the best results obtained with a three variable combination were very similar to the ones from the model that combined only weekly maximum temperature and precipitation.

The resulting smoothed predictor variables and summary statistics are showed in Appendix 9.2. It should be noted that for every variable combination, all predictor variables employed were equally statistically significant at $p < 0.001$.

Figure 4.1 to Figure 4.15 represent the predicted weekly malaria incidence from both test and validation datasets, plotted against the real observed malaria cases, for each model. As displayed in Table 4.2, the mean absolute error (MAE) associated with each model varied between 309 and 368 weekly malaria cases, which correspond to a mean absolute percentage error (MAPE) ranging from 29.5% to 35.1%.

Model I. Mal = Mal_1 + s(Tmax-8

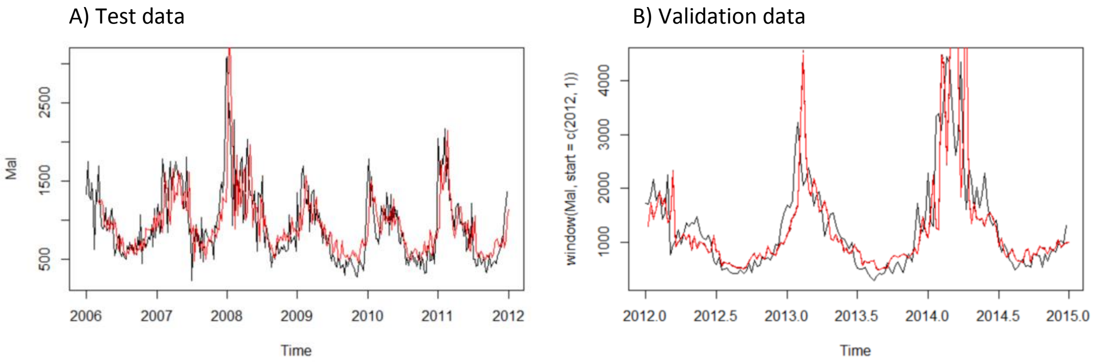

Figure 4.1 – Observed (black) vs. predicted (red) malaria cases (Model I)

Model II. Mal = Mal_1 + s(Tmin-8)

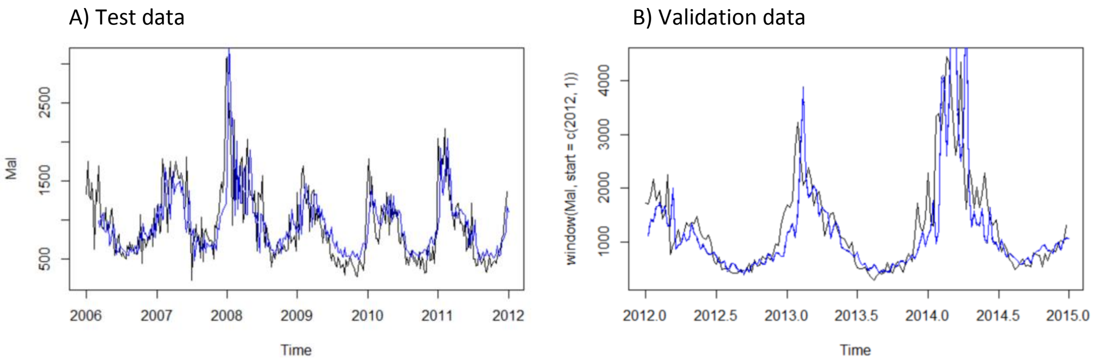

Figure 4.2 – Observed (black) vs. predicted (blue) malaria cases (Model II)

Model III. Mal = Mal_1 + s(Tmean-12)

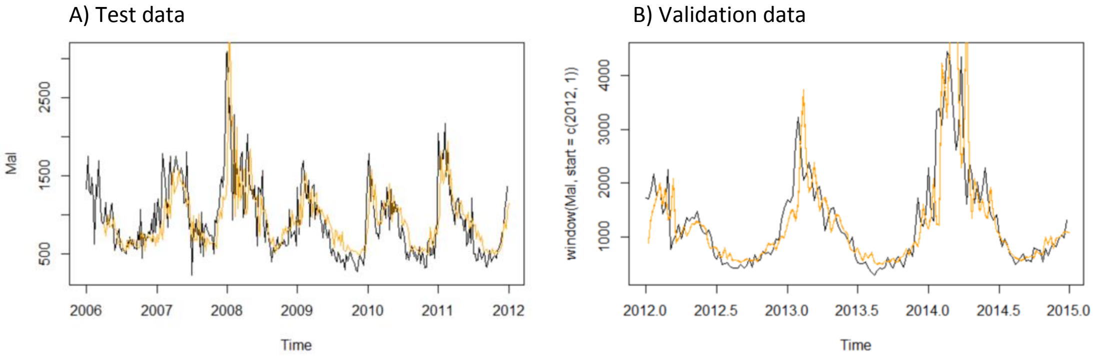

Figure 4.3 – Observed (black) vs. predicted (yellow) malaria cases (Model III)

Model IV. Mal = Mal_1 + s(RH-4)

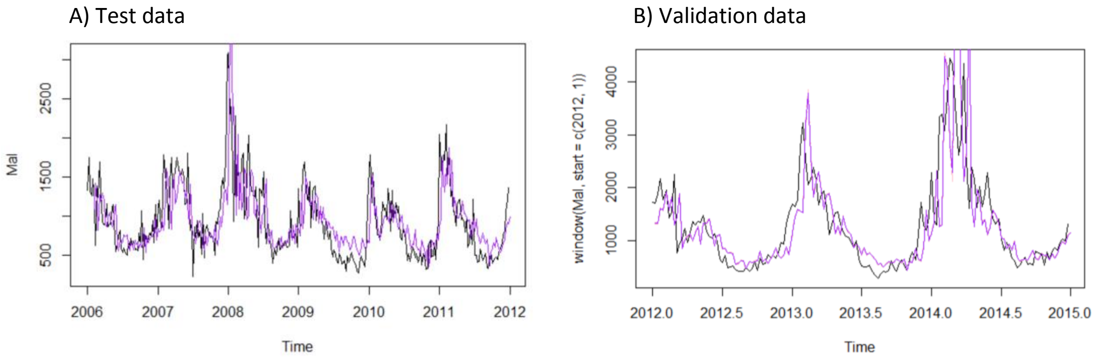

Figure 4.4 – Observed (black) vs. predicted (purple) malaria cases (Model IV)

Model V. Mal = Mal_1 + s(P-3)

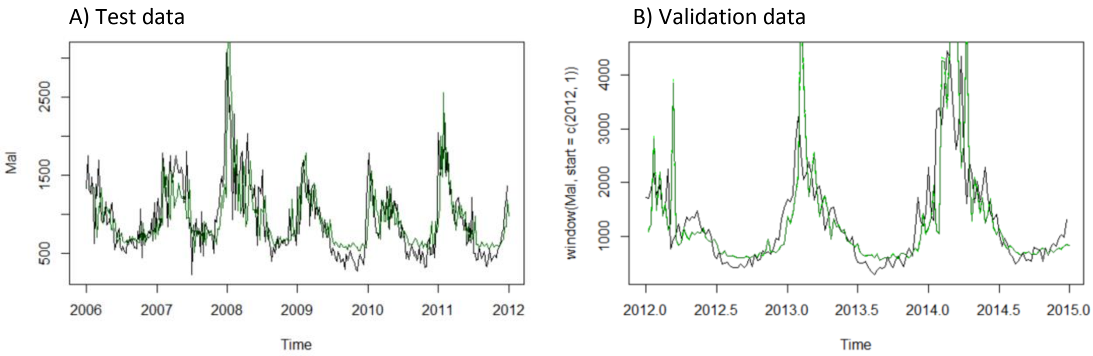

Figure 4.5 – Observed (black) vs. predicted (green) malaria cases (Model V)

Model VI. Mal = Mal_1 + s(Tmax-8) + s(RH-4)

A) Test data B) Validation data

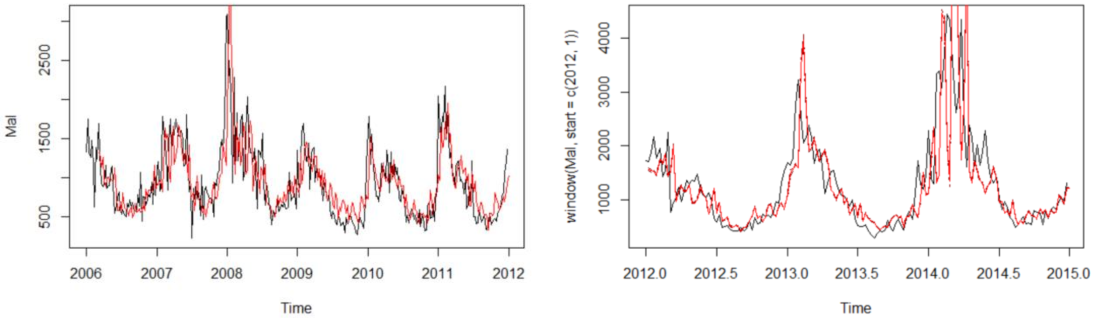

Figure 4.6 – Observed (black) vs. predicted (red) malaria cases (Model VI)

Model VII. Mal = Mal_1 + s(Tmin-7) + s(RH-4)

A) Test data B) Validation data

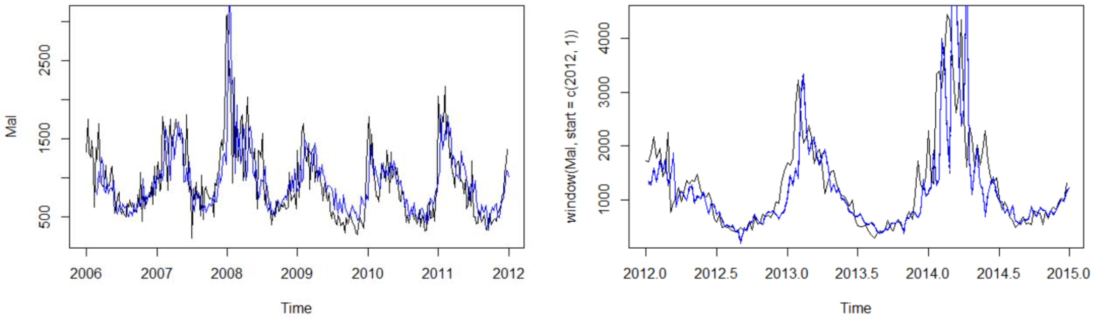

Figure 4.7 – Observed (black) vs. predicted (blue) malaria cases (Model VII)

Model VIII. Mal = Mal_1 + s(Tmean-12) + s(RH-10)

A) Test data B) Validation data

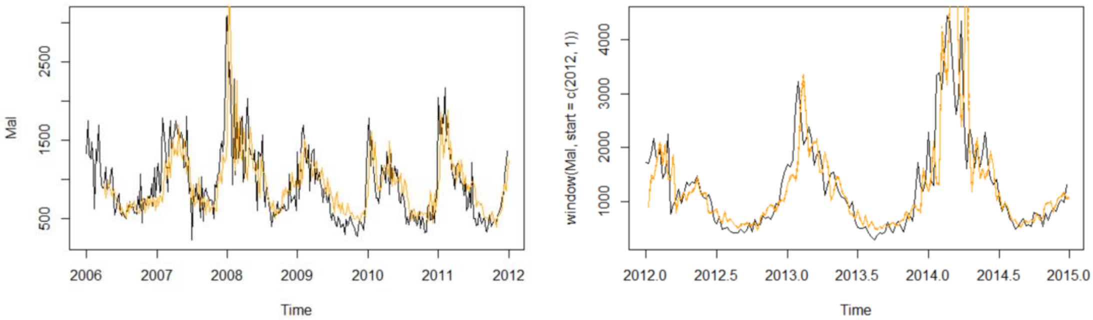

Figure 4.8 – Observed (black) vs. predicted (yellow) malaria cases (Model VIII)

Model IX. Mal = Mal_1 + s(Tmax-15) + s(P-3)

A) Test data B) Validation data

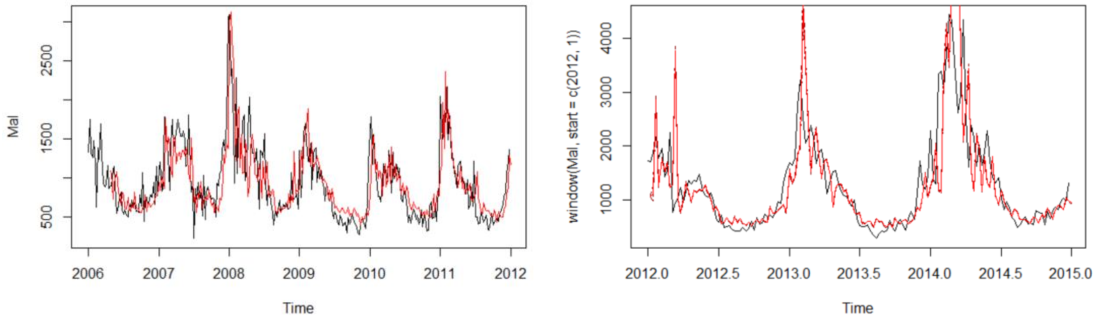

Figure 4.9 – Observed (black) vs. predicted (red) malaria cases (Model IX)

Model X. Mal = Mal_1 + s(Tmin-8) + s(P-3)

A) Test data B) Validation data

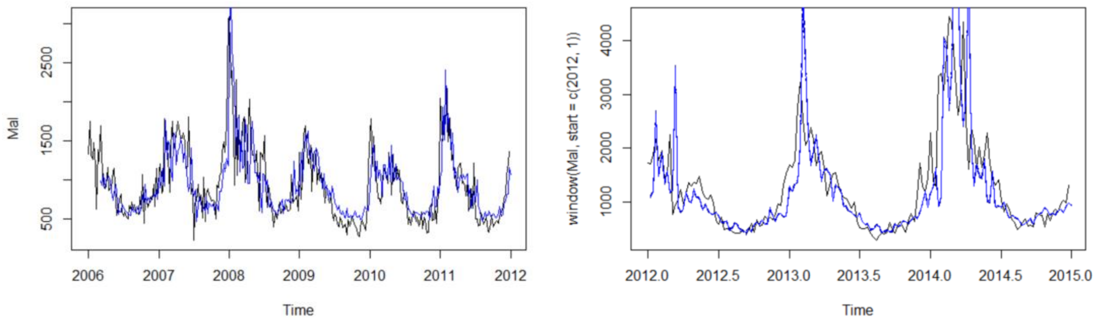

Figure 4.10 – Observed (black) vs. predicted (blue) malaria cases (Model X)

Model XI. Mal = Mal_1 + s(Tmean-12) + s(P-3)

A) Test data B) Validation data

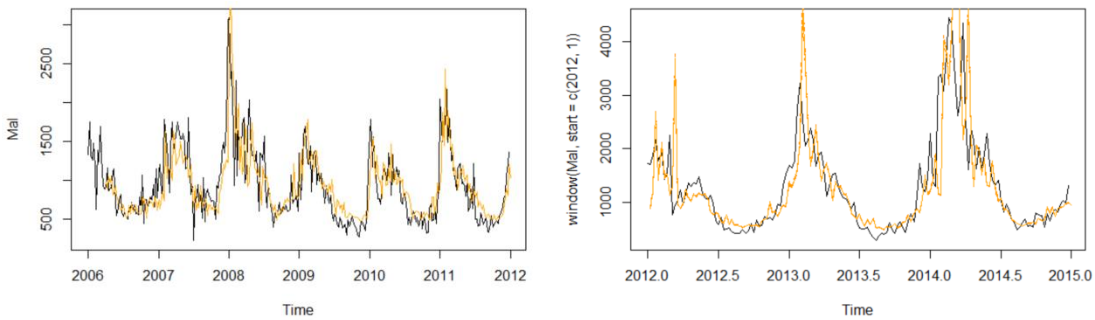

Figure 4.11 – Observed (black) vs. predicted (yellow) malaria cases (Model XI)

Model XII. Mal = Mal_1 + s(RH-2) + s(P-3)

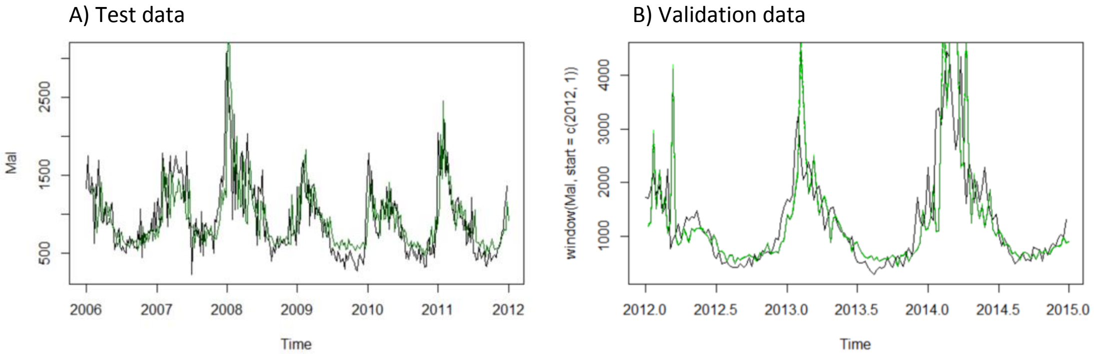

Figure 4.12 – Observed (black) vs. predicted (green) malaria cases (Model XII)

Model XIII. Mal = Mal_1 + s(Tmax-15) + s(RH-12) + s(P-3)

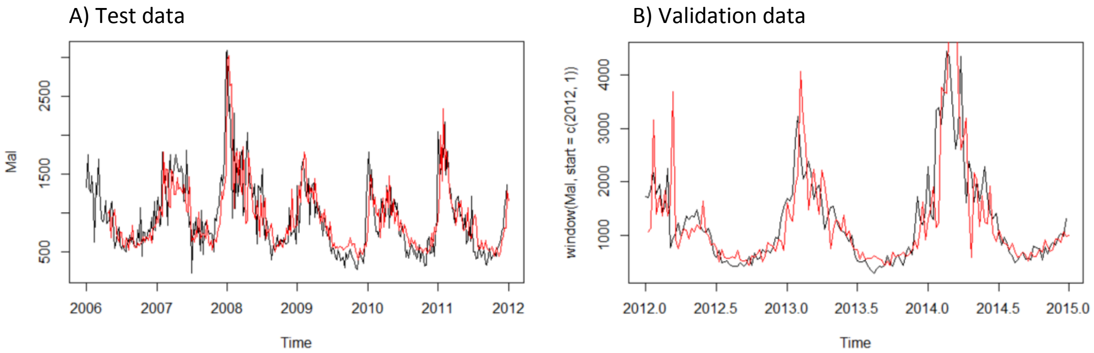

Figure 4.13 – Observed (black) vs. predicted (red) malaria cases (Model XIII)

Model XIV. Mal = Mal_1 + s(Tmin-12) + s(RH-12) + s(P-3)

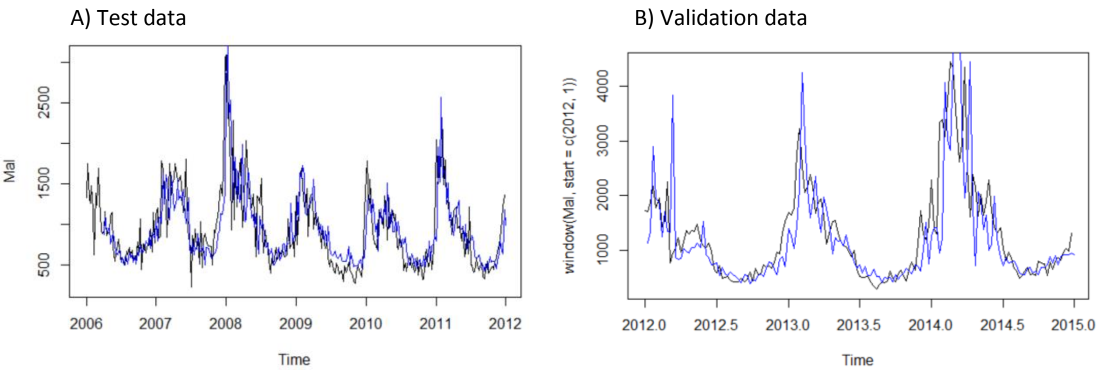

Figure 4.14 – Observed (black) vs. predicted (blue) malaria cases (Model XIV)

Model XV. Mal = Mal_1 + s(Tmean-12) + s(RH-12) + s(P-3)

A) Test data B) Validation data

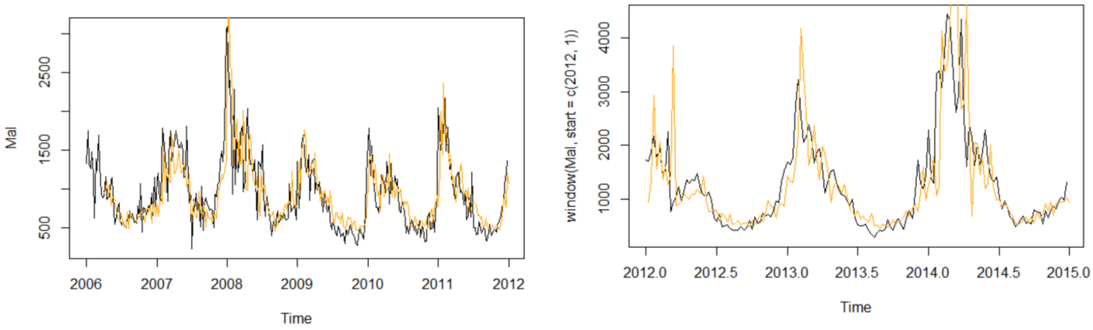

Figure 4.15 – Observed (black) vs. predicted (yellow) malaria cases (Model XV)

5. DISCUSSION

The search for predictive models of malaria incidence has been a subject of interest for more than 100 years, with progressively more complex models and new predictive variables being introduced.

The purpose of this study was to determine if a simple statistical model, using meteorological data and a single health indicator, both of which are readily available and easy to obtain, could provide accurate short-term predictions of the evolution of malaria incidence in the Chimoio district, in Mozambique.

The results have showed that, with a combination of two to three climatic variables we were able to explain more than 70% of the variability in weekly malaria incidence. These results were achieved using either a two-variable model, based on 15-week lagged maximum temperature and 3-week lagged precipitation, or a three-variable combination, employing 15-week lagged maximum temperature, 12-week lagged relative humidity and 3-week lagged precipitation.

It is not surprising that these specific meteorological variables, particularly temperature and rainfall, have been the ones more significantly associated to malaria incidence in our study, since this relationship has been consistently identified throughout the literature (Reiner et al., 2015).

Our results have also highlighted the synergy between temperature and precipitation regarding their impact on malaria transmission, since the combination of these variables resulted in the highest overall increase in the adjusted R^2.

While the majority of studies have pointed to a period between 1 to 2 months between changes in climate and its observed effects on malaria incidence, our analysis revealed a more protracted effect between changes in temperature (maximum, minimum or mean) or relative humidity and its repercussions on the evolution of malaria cases. Specifically, the most significant outcomes have been found when an interval ranging between 12 to 15 weeks has been applied to each of these variables. The impact of rainfall, on the other hand, showed a consistent significant relation with malaria incidence after three weeks.

It should be noted that most of the available literature was performed using monthly instead of weekly data and therefore may not be sensitive to variations that occur bellow a 4-week interval.

Regarding the use of different temperature measurements, no significant differences were found between the results from equivalent models using either maximum, minimum or mean temperatures.

Given that the range of annual temperatures in Chimoio is limited and remains mostly within suitable limits that allow for perennial malaria transmission, this could be the reason why there is not a significant discriminative power between distinct temperature metrics and malaria incidence in this region. Possibly in a non-endemic area, where annual temperature ranges are more pronounced, the differences in the impact of these three variables regarding both parasite and vector development could be more prominent.

The same reasoning can be applied to relative humidity, in the sense that it is consistently high in Chimoio and therefore usually above the 60% threshold for optimal mosquito development.

Consequently, in this study the addition of relative humidity to the models did not result in a significant improvement in the final outcomes. These results are in accordance with previous findings published by Ferrão et al. (2017a), demonstrating that relative humidity does not seem to significantly impact malaria incidence in Chimoio.

However, it should be noted that for every tested model, all the predictor variables were equally statistically significant, with a p-value below 0.001. Further details regarding the model's statistics can be found in Appendix 9.2.

When the models were tested against the validation dataset, the resulting MAE varied between 309 and 368 weekly malaria cases, which correspond to a MAPE ranging from 29.5% to 35.1%. Although this is not an ideal result, one should acknowledge that attempting to predict malaria incidence based solely on three climacteric variables is undoubtedly an oversimplification of a very complex process, which to this day has not been fully understood.

There are multiple other contributing factors, either of biological, epidemiologic or environmental nature that can influence malaria transmission and might play an important role in this particular location. For example, socioeconomic status is already known to influence malaria risk in Mozambique (INE, 2013b). Moreover, in most endemic areas of malaria, changes in social and economic conditions have been identified as being of much greater importance than temperature shifts (Yang & Ferreira, 2000).

Nevertheless, despite the differences obtained between observed and predicted cases, the predicted values seem to effectively follow the upward and downward trends in malaria incidence, which is an important indicator in itself as it allows adequately allocating resources and deploying preventative strategies in advanced.

6. CONCLUSIONS

This study adds to the growing body of knowledge confirming that climatic variables are significant drivers of malaria incidence and transmission and can provide meaningful information that allows for the anticipation of outbreaks within in a relatively short time period.

By applying a relatively simple methodology, that combines temperature, relative humidity and precipitation, as well as the most recent number of reported malaria cases, we were able to develop a predictive model that quite accurately represents the observed trends of malaria incidence in Chimoio, over different years.

This is a straightforward and economical approach, supported by meteorological and epidemiologic data that are already presently collected and therefore easy to incorporate in a simple predictive model, that could potentially be applied by local health authorities in order to predict malaria outbreaks. With this information, adequate preventative interventions and resource allocation can be planned and deployed within a more reasonable time frame.

Furthermore, if deemed appropriate, this model could also be tested and validated for other endemic or non-endemic regions and provide some further benefits in reducing the burden posed by malaria worldwide.

7. LIMITATIONS AND RECOMMENDATIONS FOR FUTURE WORKS

The difficulty in obtaining quality data is a recurrent issue for researchers. As Hoshen and Morse (2004) have previously highlighted, high quality meteorological data at the pan-African level is not available, given the irregular positioning of stations and the occurrence of frequently missing measurements.

Furthermore, the lack of access to health services is known to result in under-reporting of cases and over-diagnosis of malaria, which often confounds correlations (Lindsay, Parson, & Thomas, 1998; Snow et al., 1998).

As such, the lack of further available data prevents additional developments on this particular model. If a larger time period could be used in order to perform both the testing and validation steps, possibly the results could be optimized. Additionally, the inclusion of other variables such as vegetation coverage, distance to water bodies, demographic data or the use of bed nets could improve the quality of the predictions.

Another limitation of this study is that these results have been specifically tailored around a particular region of the globe and may not be reproducible when applied to other locations due to incomplete parameterization of factors that influence the geographical range and intensity of malaria transmission in specific regions (Confalonieri et al., 2007).

In contrast, the simplicity of this approach makes it an attractive option to apply to larger and more complex malaria databases, where it might contribute to clarify specific contexts of malaria transmission.

In fact, several authors have previously defended that a regional analysis is inevitably necessary since the horizontal resolution of the underlying climate projection is mostly inadequate and neglects local features (Ermert, 2009; Githeko et al., 2000; McMichael, 1997).

Therefore, with the increase of computational power, perhaps future research could focus on the development of risk models specifically designed for regional settings instead of a global approach.

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9. APPENDIXES

9.1. OVERVIEW OF PUBLICATIONS EVALUATING THE ASSOCIATION BETWEEN MALARIA DISEASE AND ENVIRONMENTAL/CLIMATIC VARIABLES EMPLOYING THE MOST FREQUENTLY USED STATISTICAL METHODS

Table 9.1 – Overview of publications investigating malaria disease and environmental/climatic variables employing the most frequently used statistical methods (Adapted from Ebhuoma & Gebreslasie, 2016 and Reiner et al., 2015)

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Abeku et al. (2004)	Effects of meteorological factors on epidemic malaria in Ethiopia: a statistical modeling approach based on theoretical reasoning	Ethiopia	Rainfall, Temperature	Linear mixed model
Abellana et al. (2008)	Spatio-seasonal modeling of the incidence rate of malaria in Mozambique	Mozambique	Rainfall, Temperature	Hierarchical bayesian
Ageep et al. (2009)	Spatial and temporal distribution of the malaria mosquito Anopheles arabiensis in northern Sudan: influence of environmental factors and implications for vector control	Sudan	River level, Temperature	Regression
Amek et al. (2012)	Spatial and temporal dynamics of malaria transmission in rural Western Kenya	Kenya	Elevation, Normalized Difference Vegetation Index (NVDI), Rainfall, Temperature	Spatio-temporal
Balls et al. (2004)	Effect of topography on the risk of malaria infection in the Usambara Mountains, Tanzania	Tanzania	Topography	Logistic regression
Bantje, (1987)	Seasonality of births and birth-weights in Tanzania	Tanzania	Rainfall	Lagged regression
Bayoh, Thomas and Lindsay (2001)	Mapping distributions of chromosomal forms of Anopheles gambiae in West Africa using climate data	West Africa	Evapotranspiration, Rainfall, Temperature	Logistic regression
Bi et al. (2003)	Climatic variables and transmission of malaria: A 12-year data analysis in Shuchen County, China	China	Rainfall, Relative humidity, Temperature	Autoregressive Integrated Moving Average (ARIMA), Generalized Least Square (GLS) regression
Briët et al. (2008)	Temporal correlation between malaria and rainfall in Sri Lanka	Sri Lanka	Rainfall	Correlation and regression

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Briët, Vounatsou and Amerasinghe (2008)	Malaria seasonality and rainfall seasonality in Sri Lanka are correlated in space	Sri Lanka	Rainfall	Seasonal Autoregressive Integrated Moving Average (SARIMA), Conditional Auto-Regressive (CAR) model
Clements et al. (2009)	Space-time variation of malaria incidence in Yunnan province, China	China	Rainfall, Temperature	Bayesian Poisson regression models
Cohen et al. (2013)	Rapid case-based mapping of seasonal malaria transmission risk for strategic elimination planning in Swaziland	Swaziland	Distance to water bodies, Rainfall, Temperature, Vegetation indices	Logistic regression mixed model, Random forest
Cottrell et al. (2012)	Modeling the Influence of Local Environmental Factors on Malaria Transmission in Benin and Its Implications for Cohort Study	Benin	NVDI, Rainfall	Three-level Poisson mixed regression model
Craig et al. (2004)	Exploring 30 years of malaria case data in KwaZulu-Natal, South Africa: Part I. The impact of climatic factors	South Africa	Rainfall, Temperature	Linear regression
Craig et al. (2007)	Developing a spatial-statistical model and map of historical malaria prevalence in Botswana using a staged variable selection procedure	Botswana	Elevation, NDVI, Rainfall, Surface water land cover, Temperature, Vapour pressure	Logistic regression
Drakeley et al. (2005)	Altitude-dependent and -independent variations in Plasmodium falciparum prevalence in northeastern Tanzania	Tanzania	Rainfall	Regression
Gao et al. (2012)	Change in Rainfall Drives Malaria Re-Emergence in Anhui Province, China	China	Rainfall	Polynomial distributed lag time-series regression (Distributed Lag Non-Linear Model [DLNM])
Gaudart et al. (2009)	Modelling malaria incidence with environmental dependency in a locality of Sudanese savannah area, Mali	Mali	NDVI	ARIMA
Gomez-Elipe et al. (2007)	Forecasting malaria incidence based on monthly case reports and environmental factors in Karuzi, Burundi, 1997–2003	Burundi: Karuzi	NVDI, Rainfall, Temperature	ARIMA

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Gosoniu et al. (2012)	Spatially explicit burden estimates of malaria in Tanzania: Bayesian geostatistical modeling of the malaria indicator survey data	Tanzania	Altitude, NDVI, Rainfall, Temperature, Water bodies	Multivariate logistic regression, Bayesian kriging
Gosoniu, Veta and Vounatsou (2010)	Bayesian geostatistical modeling of Malaria Indicator Survey data in Angola	Angola	Altitude, NDVI, Rainfall, Temperature	Bayesian logistic regression, Bayesian kriging
Gosoniu et al. (2009)	Mapping malaria risk in West Africa using a Bayesian nonparametric non-stationary model	West Africa	Agro-ecological zones, Altitude, Land use, NDVI, Rainfall, Soil Water Storage (SWS) index, Temperature, Water bodies	Logistic and non-parametric regression
Gosoniu et al. (2006)	Bayesian modelling of geostatistical malaria risk data	Mali	Rainfall, Season length, Temperature, Water bodies	Bayesian logistic regression, Bayesian non-stationary model, Bayesian kriging
Graves et al. (2008)	Effectiveness of malaria control during changing climate conditions in Eritrea, 1998-2003	Eritrea	NVDI, Rainfall	Poisson regression
Haghdoost, Alexander and Cox (2008)	Modelling of malaria temporal variations in Iran	Iran	Humidity, Rainfall, Temperature, Visibility, Wind speed	Poisson regression
Haque et al. (2010)	The Role of Climate Variability in the Spread of Malaria in Bangladeshi Highlands	Bangladesh	El Niño Southern Oscillation (ENSO) [1], Humidity, Rainfall, Temperature	Generalized linear negative binomial regression
Hashizume, Terao and Minakawa (2009)	The Indian Ocean Dipole and malaria risk in the highlands of western Kenya	Kenya	Indian Ocean Dipole (IOD)[2], Rainfall	Poisson regression (Generalized Linear Model [GLM])

[1] The El Niño-Southern Oscillation (ENSO) is a recurring climate pattern involving changes in the temperature of waters in the central and eastern tropical Pacific Ocean. On periods ranging from about three to seven years, the surface waters across a large swath of the tropical Pacific Ocean warm or cool by anywhere from 1°C to 3°C, compared to normal. This oscillating warming and cooling pattern, referred to as the ENSO cycle, directly affects rainfall distribution in the tropics and can have a strong influence on weather across the globe (United States National Weather Service, n.d)

[2] The Indian Ocean Dipole (IOD) measures differences in sea surface temperatures between the Arabian Sea (western pole) and the eastern Indian Ocean south of Indonesia (eastern pole). Like ENSO, IOD is a coupled ocean-atmosphere phenomenon where the shifting pools of warm/cool water contribute to variations in rainfall and storm activities of many countries surrounding the Indian Ocean (Paul & Rashid, 2017).

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Jackson et al. (2010)	Modelling the effect of climate change on prevalence of malaria in western Africa	West Africa	Atmospheric pressure, Rainfall, Temperature, Vapour pressure	Spatial regression
Jacob et al. (2007)	Remote and field level quantification of vegetation covariates for malaria mapping in three rice agro-village complexes in Central Kenya	Kenya	Vegetation indices	Logistic regression
Jones and Morse (2010)	Application and Validation of a Seasonal Ensemble Prediction System Using a Dynamic Malaria Model	Botswana	Rainfall, Temperature	Multimodel ensemble system
Jones and Morse (2012)	Skill of ENSEMBLES seasonal re-forecasts for malaria prediction in West Africa	Cameroon	Rainfall, Temperature	Multimodel ensemble system
Jones et al. (2007)	Climate prediction of El Nino malaria epidemics in north-west Tanzania	Tanzania	ENSO, Rainfall, Temperature	Regression
Kalinga-Chirwa et al. (2011)	Linking rainfall and irrigation to clinically reported malaria cases in some villages in Chikhwawa District, Malawi	Malawi	Rainfall	GLM
Kazembe, Kleinschmidt and Sharp (2006)	Patterns of malaria-related hospital admissions and mortality among Malawian children: an example of spatial modelling of hospital register data	Malawi	Wet/Dry seasons	Logistic and Poisson regression (spatial)
Kazembe et al. (2008)	Applications of Bayesian approach in modelling risk of malaria-related hospital mortality	Malawi	Wet/Dry seasons	Semiparametric regression models (Markov Chain Monte Carlo [MCMC])
Kim, Park and Cheong (2012)	Estimated Effect of Climatic Variables on the Transmission of Plasmodium vivax Malaria in the Republic of Korea	Korea	Rainfall, Relative humidity, Temperature	GLM (Poisson); DLNM
Kleinschmidt et al. (2001)	Use of generalized linear mixed models in the spatial analysis of small-area malaria incidence rates in KwaZulu Natal, South Africa	South Africa	Rainfall, Temperature	Generalized Linear Mixed Model (GLMM)
Kleinschmidt et al. (2000)	A spatial statistical approach to malaria mapping	Mali	Distance to water bodies, NVDI, Rainfall, Temperature	Logistic regression, Kriging
Lafferty (2009)	The ecology of climate change and infectious diseases	Poland	Rainfall	Log-linear regression

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Loha and Lindtjørn (2010)	Model variations in predicting incidence of Plasmodium falciparum malaria using 1998-2007 morbidity and meteorological data from south Ethiopia	Ethiopia	Rainfall, Relative humidity, Temperature	ARIMA
Lowe, Chirombo and Tompkins (2013)	Relative importance of climatic, geographic and socio-economic determinants of malaria in Malawi	Malawi	Altitude, Rainfall, Temperature	GLM, GLMM, Kernel density
Mabaso et al. (2005)	Towards empirical description of malaria seasonality in southern Africa: the example of Zimbabwe	Zimbabwe	NDVI, Rainfall, Temperature, Vapour pressure	Bayesian Poisson model
Mabaso et al. (2007)	Environmental predictors of the seasonality of malaria transmission in Africa: the challenge	Sub-Saharan Africa	Rainfall, Temperature	Multiple stepwise linear regression
Midekisa et al. (2012)	Remote sensing-based time series models for malaria early warning in the highlands of Ethiopia	Ethiopia: Amhara	Evapotranspiration, Temperature, Vegetation indices	SARIMA
Nkurunziza, Gebhardt and Pilz (2010)	Bayesian modelling of the effect of climate on malaria in Burundi	Burundi	Humidity, Rainfall, Temperature	Bayesian inference and MCMC based on GLM and Generalized Additive Mixed Effects Model (GAMM)
Nkurunziza, Gebhardt and Pilz (2011)	Geo-additive modelling of malaria in Burundi	Burundi	Humidity, Rainfall, Temperature	Semi-parametric regression (Bayesian inference and MCMC)
Noor et al. (2008)	Spatial prediction of Plasmodium falciparum prevalence in Somalia	Somalia	Distance to water bodies, Enhanced Vegetation Index (EVI), Rainfall, Temperature	Logistic regression
Rahman et al. (2011)	Modelling and prediction of malaria vector distribution in Bangladesh from remote-sensing data	Bangladesh	Vegetation indices	Correlation and regression
Raso et al. (2012)	Mapping malaria risk among children in Cote d'Ivoire using Bayesian geo-statistical models	Côte d'Ivoire	Distance to water bodies, NVDI, Rainfall, Temperature	Bayesian logistic regression, Bayesian regression, Bayesian kriging
Raso et al. (2009)	Spatial risk profiling of Plasmodium falciparum parasitaemia in a high endemicity area in Cote d'Ivoire	Côte d'Ivoire	Elevation, NVDI, Rainfall, Temperature	Bayesian negative binomial regression models, Bayesian kriging

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Reid et al. (2012)	Characterizing the spatial and temporal variation of malaria incidence in Bangladesh, 2007	Bangladesh	Rainfall, Temperature	Bayesian poisson regression
Riedel et al. (2010)	Geographical patterns and predictors of malaria risk in Zambia: Bayesian geostatistical modelling of the 2006 Zambia National Malaria Indicator Survey (ZMIS)	Zambia	Altitude, Land cover, NDVI, Rainfall, Temperature, Water bodies	Bivariate and multiple regression analysis, Bayesian kriging
Silué et al. (2008)	Spatially-explicit risk profiling of Plasmodium falciparum infections at a small scale: A geostatistical modelling approach	Côte d'Ivoire	Distance to nearest river, NVDI, Rainfall, Temperature	Bivariate logistic regression
Small et al. (2003)	Climatic suitability for malaria transmission in Africa, 1911-1995	Africa	Rainfall, Temperature	Ordinary Least-Squares regression with Autoregressive error structure
Sogoba et al. (2007)	The spatial distribution of Anopheles gambiae sensu stricto and An. arabiensis (Diptera : Culicidae) in Mali	Mali	Distance to water bodies, NDVI, Rainfall, SWS index, Temperature	Bayesian geostatistical logistic regression
Teklehaimanot et al. (2004a)	Weather-based prediction of Plasmodium falciparum malaria in epidemic-prone regions of Ethiopia I. Patterns of lagged weather effects reflect biological mechanisms	Ethiopia: Highlands	Rainfall, Temperature	Poisson regression, polynomial distributed lag model
Teklehaimanot et al. (2004b)	Weather-based prediction of Plasmodium falciparum malaria in epidemic-prone regions of Ethiopia II. Weather-based prediction systems perform comparably to early detection systems in identifying times for interventions	Ethiopia: Highlands	Rainfall, Temperature	Regression
Thomson et al. (2005)	Use of rainfall and sea surface temperature monitoring for malaria early warning in Botswana	Botswana	Rainfall, Sea Surface Temperature (SST)	Logistic regression and correlations
Thomson et al. (2006)	Malaria early warnings based on seasonal climate forecasts from multi-model ensembles	Botswana	Rainfall	Multi-model ensemble
Tian et al. (2008)	One-year delayed effect of fog on malaria transmission: a time-series analysis in the rain forest area of Mengla County, south-west China	South-West China: Mengla count	Fog day frequency, Rainfall, Relative humidity, Temperature	ARIMA

Table 9.1 – Cont.

Reference	Title	Study area	Climatic/Environmental Variables	Statistical method
Zacarias and Andersson (2010)	Mapping malaria incidence distribution that accounts for environmental factors in Maputo Province - Mozambique	Mozambique: Maputo provinc	Rainfall, Temperature	Bayesian hierarchical; MCMC
Zacarias and Andersson (2011)	Spatial and temporal patterns of malaria incidence in Mozambique	Mozambique: Maputo province	Rainfall, Relative humidity, Temperature	Bayesian with interaction terms; MCMC
Zayeri, Salehi and Pirhosseini (2011)	Geographical mapping and Bayesian spatial modeling incidence in Sistan and Baluchistan province, Iran	Iran: Baluchistand, Sistan	Elevation, Humidity, Rainfall, Temperature	GLMM, stationary kriging and variogram
Zhang, Bi and Hiller (2010)	Meteorological variables and malaria in a Chinese temperate city: A twenty-year time-series data analysis	China: Jinan	Air pressure, Humidity, Rainfall, Temperature	SARIMA
Zhang et al. (2012)	Spatial-temporal analysis of malaria and the effect of environmental factors on its incidence in Yongcheng, China, 2006-2010	China: Yongcheng	Duration of sunshine, Rainfall, Relative humidity, Temperature, Wind velocity	Multivariate analysis using a Generalized Estimating Equation (GEE) approach
Zhou et al. (2004)	Association between climate variability and malaria epidemics in the East African highlands	Ethiopia, Kenya, Uganda	Rainfall, Temperature	Non-linear mixed models

ARIMA: Autoregressive Integrated Moving Average; CAR: Conditional Auto-Regressive; DLNM: Distributed Lag Nonlinear Model; ENSO: El Niño Southern Oscillation; EVI: Enhanced Vegetation Index; GEE: Generalized Estimating Equation; GLM: Generalized Linear Model; IOD: Indian Ocean Dipole; GAMM: Generalized Additive Mixed Effects Model; GLMM: Generalized Linear Mixed Model; GLS: Generalized Least Square; MCMC: Markov Chain Monte Carlo; NVDI: Normalized Difference Vegetation Index; SARIMA: Seasonal Autoregressive Integrated Moving Average; SST: Sea Surface Temperature; SWS: Soil Water Storage; ZMIS: Zambia National Malaria Indicator Survey

9.2. SMOOTHED PREDICTOR VARIABLES AND SUMMARY STATISTICS

Model I. Mal = Mal_1 + s(Tmax-8)

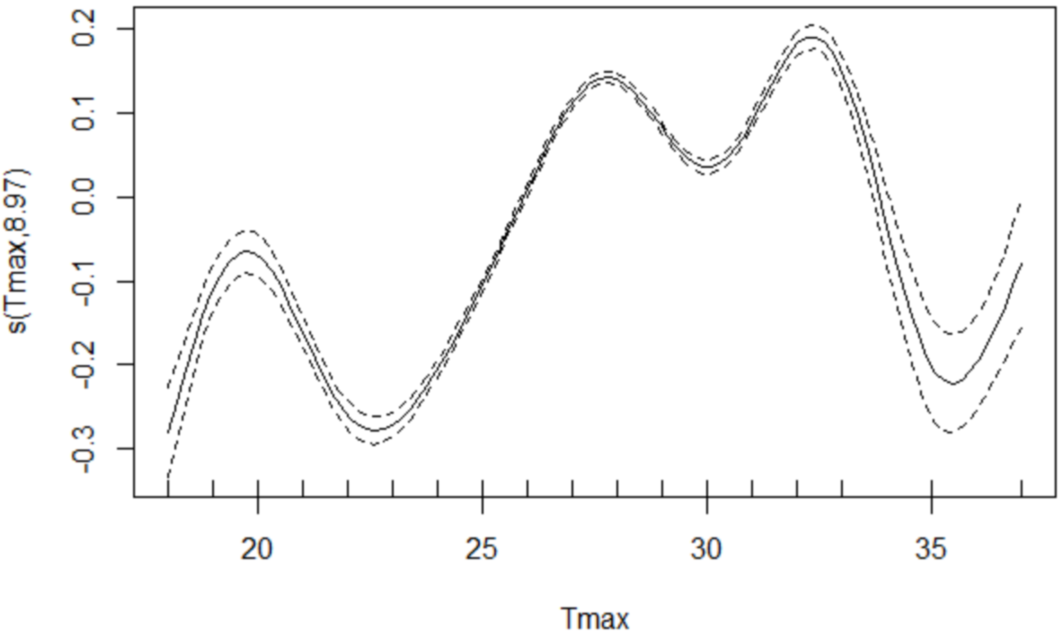

Figure 9.1 – Smoothed weekly maximum temperatures (Model I)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmax)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.200e+00  4.277e-03  1449.7   <2e-16 ***
Mal_1       6.176e-04  3.531e-06   174.9   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmax) 8.968      9   4019  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.604   Deviance explained = 64.4%
UBRE = 78.265  Scale est. = 1         n = 312
```

Figure 9.2 – Summary statistics (Model I)

Model II. Mal = Mal_1 + s(Tmin-8)

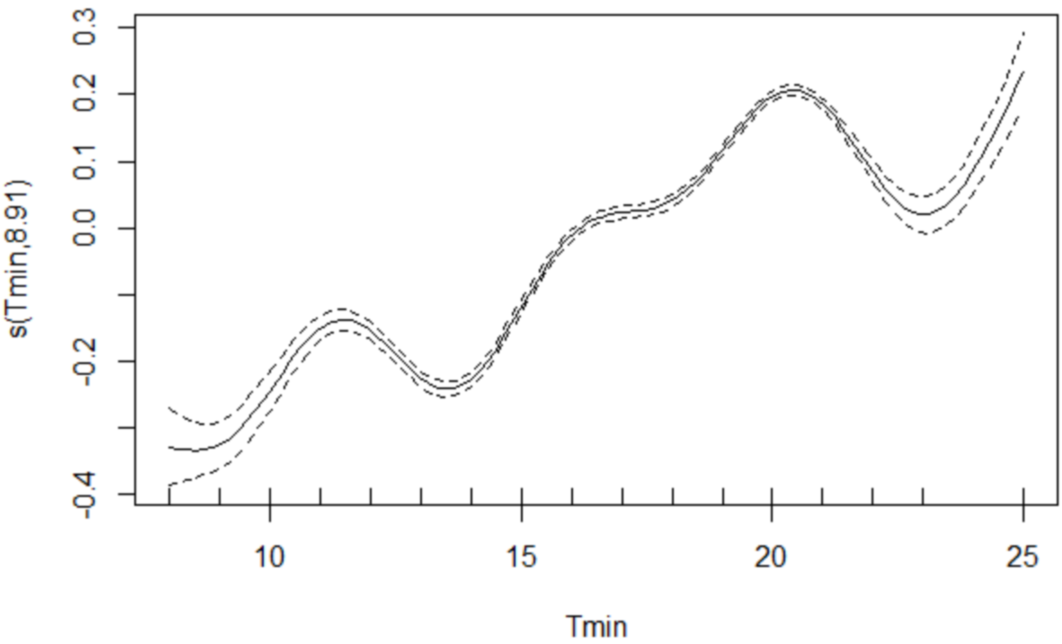

Figure 9.3 – Smoothed weekly minimum temperatures (Model II)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmin)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.271e+00  4.584e-03    1368   <2e-16 ***
Mal_1       5.330e-04  4.070e-06     131   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmin) 8.909  8.997   4675  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.598   Deviance explained = 63.9%
UBRE = 75.806  Scale est. = 1         n = 304
```

Figure 9.4 – Summary statistics (Model II)

Model III. Mal = Mal_1 + s(Tmean-12)

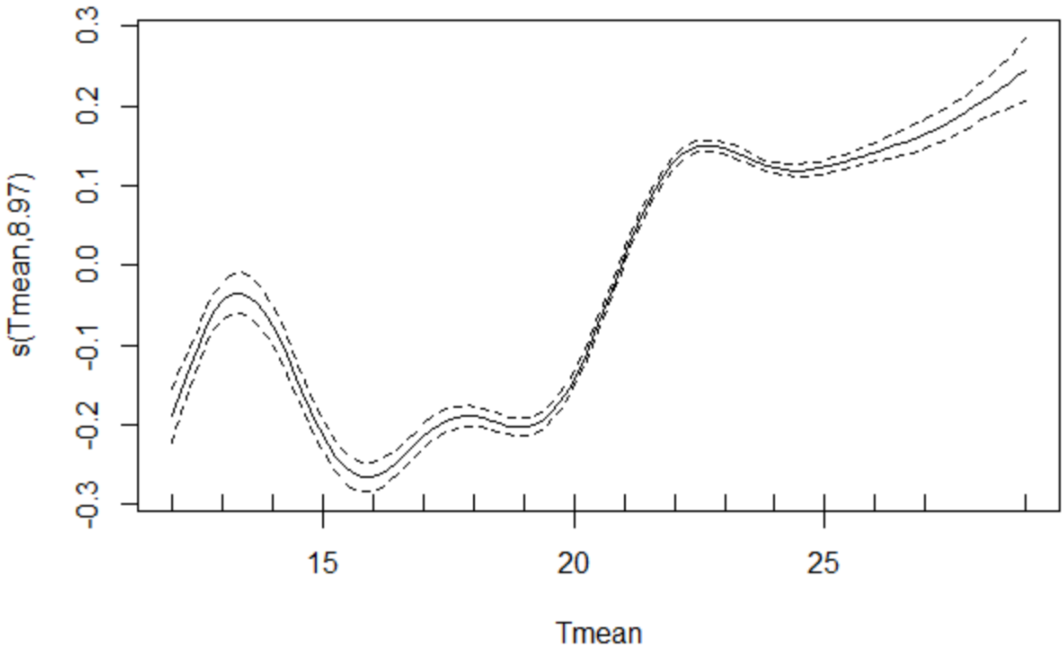

Figure 9.5 – Smoothed weekly mean temperatures (Model III)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmean)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.251e+00  4.411e-03  1417.1   <2e-16 ***
Mal_1       5.528e-04  3.845e-06   143.8   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(Tmean) 8.965      9   4334  <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) =   0.59   Deviance explained = 63.5%
UBRE = 76.755  Scale est. = 1         n = 300
```

Figure 9.6 – Summary statistics (Model III)

Model IV. Mal = Mal_1 + s(RH-4)

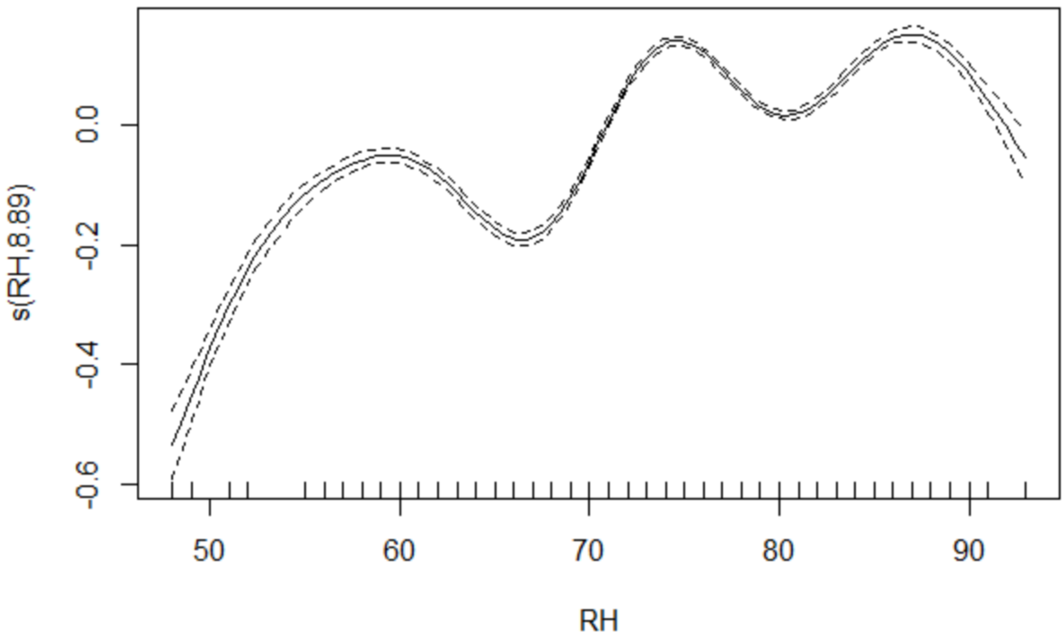

Figure 9.7 – Smoothed weekly relative humidity (Model IV)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(RH)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.208e+00  4.603e-03  1348.7   <2e-16 ***
Mal_1       6.139e-04  3.979e-06   154.3   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
        edf Ref.df Chi.sq p-value
s(RH) 8.887  8.996   3011  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.563   Deviance explained = 61.4%
UBRE =  83.27  Scale est. = 1         n = 312
```

Figure 9.8 – Summary statistics (Model IV)

Model V. Mal = Mal_1 + s(P-3)

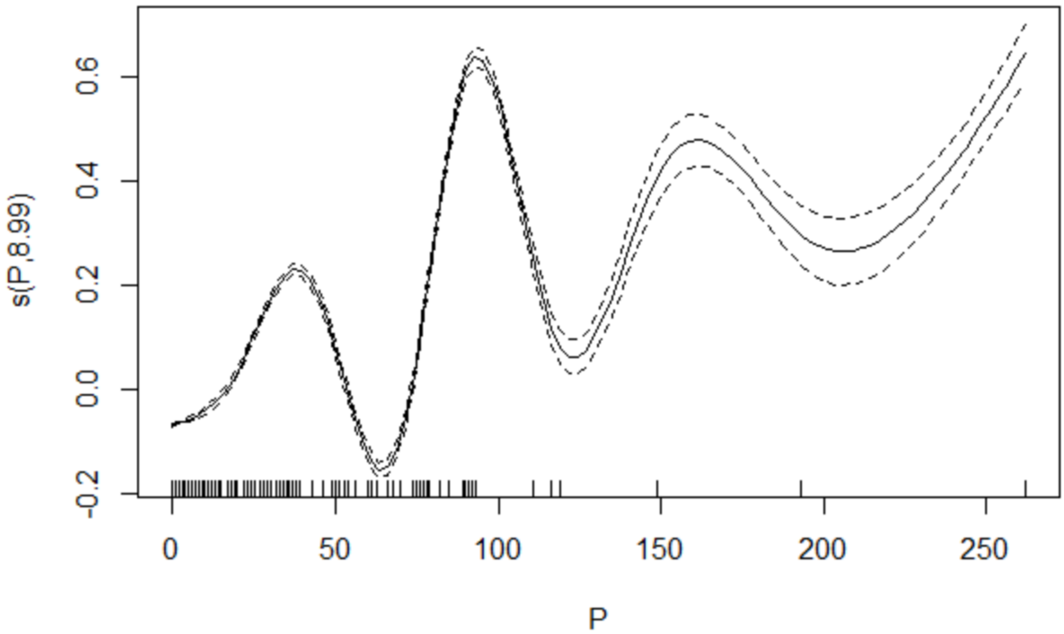

Figure 9.9 – Smoothed weekly precipitation (Model V)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.180e+00  4.544e-03  1359.9   <2e-16 ***
Mal_1       6.380e-04  3.887e-06   164.1   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
       edf Ref.df Chi.sq p-value
s(P) 8.991      9   8045  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.653   Deviance explained = 67.1%
UBRE = 69.673  Scale est. = 1         n = 312
```

Figure 9.10 – Summary statistics (Model V)

Model VI. Mal = Mal_1 + s(Tmax-8) + s(RH-4)

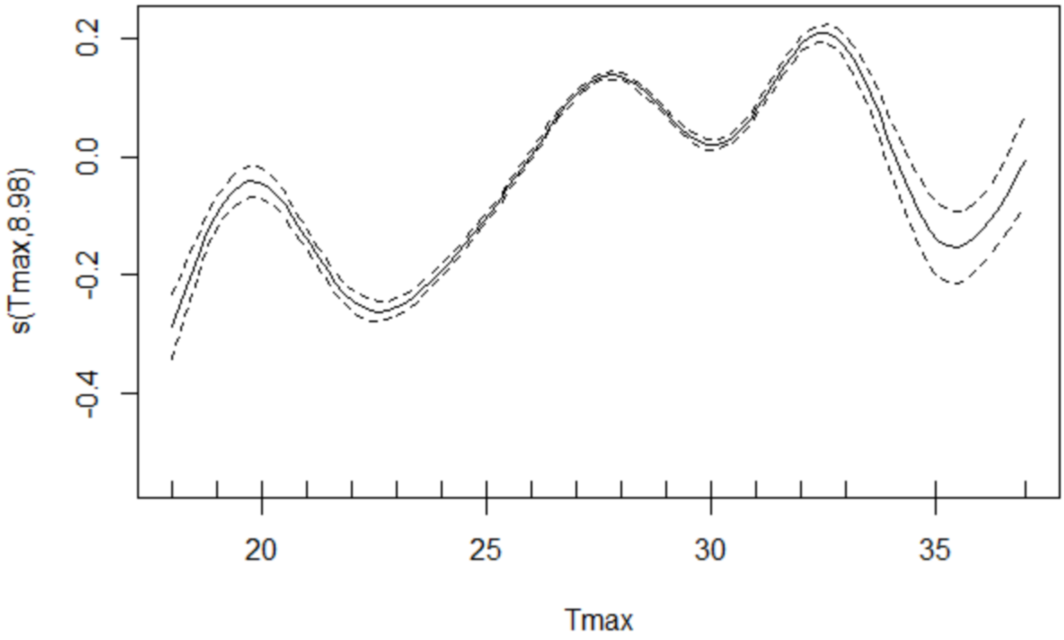

Figure 9.11 – Smoothed weekly maximum temperatures (Model VI)

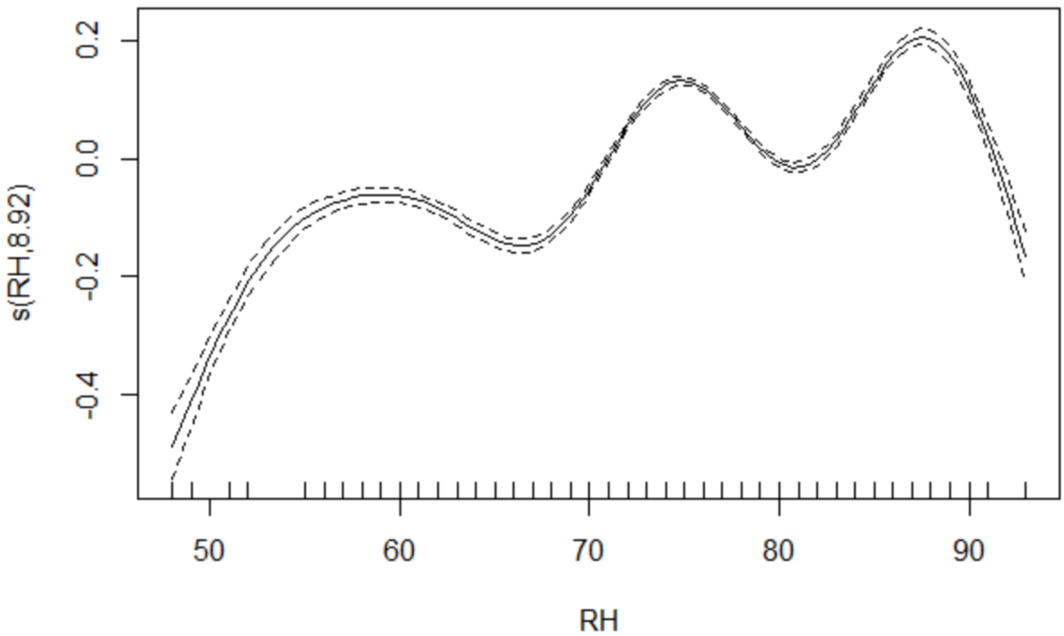

Figure 9.12 – Smoothed weekly relative humidity (Model VI)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmax) + s(RH)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.247e+00  4.756e-03  1313.5   <2e-16 ***
Mal_1       5.622e-04  4.172e-06   134.8   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmax) 8.978  9.000   3630  <2e-16 ***
s(RH)   8.923  8.998   2704  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.635   Deviance explained = 68.4%
UBRE =  69.45  Scale est. = 1         n = 312
```

Figure 9.13 – Summary statistics (Model VI)

Model VII. Mal = Mal_1 + s(Tmin-7) + s(RH-4)

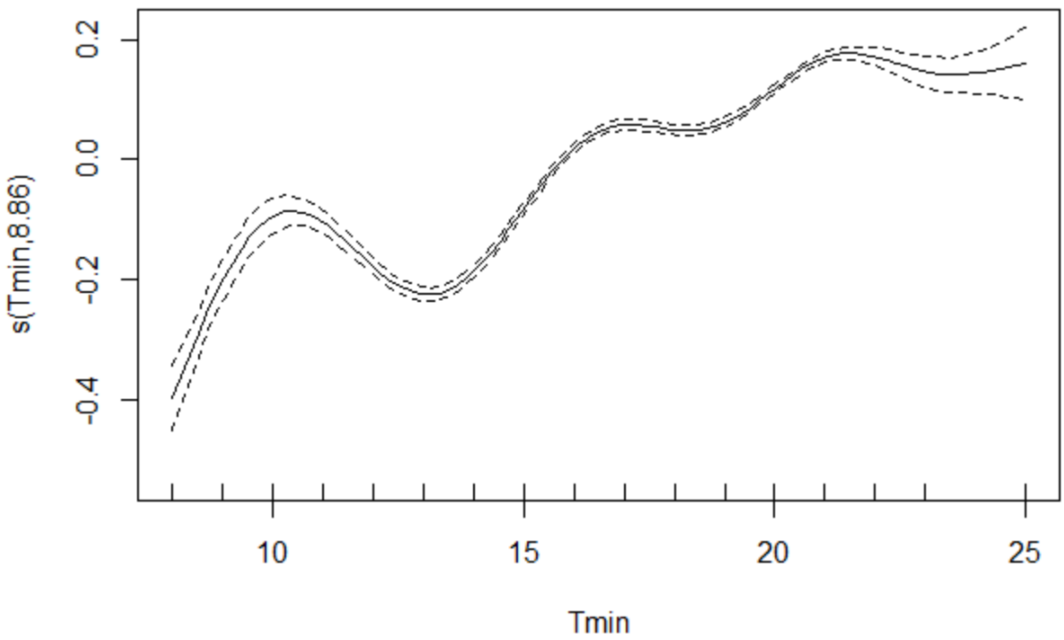

Figure 9.14 – Smoothed weekly minimum temperatures (Model VII)

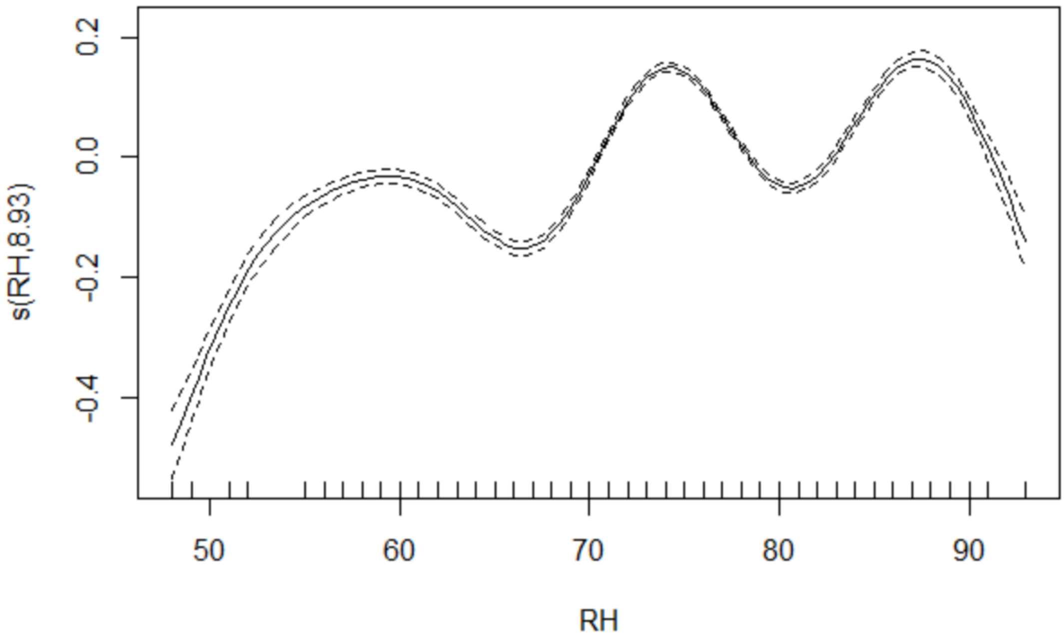

Figure 9.15 – Smoothed weekly relative humidity (Model VII)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmin) + s(RH)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.280e+00  4.762e-03  1318.9   <2e-16 ***
Mal_1       5.292e-04  4.221e-06   125.4   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmin) 8.859  8.993   3297  <2e-16 ***
s(RH)   8.925  8.998   2382  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.619   Deviance explained = 67.4%
UBRE = 71.421  Scale est. = 1         n = 312
```

Figure 9.16 – Summary statistics (Model VII)

Model VIII. Mal = Mal_1 + s(Tmean-12) + s(RH-10)

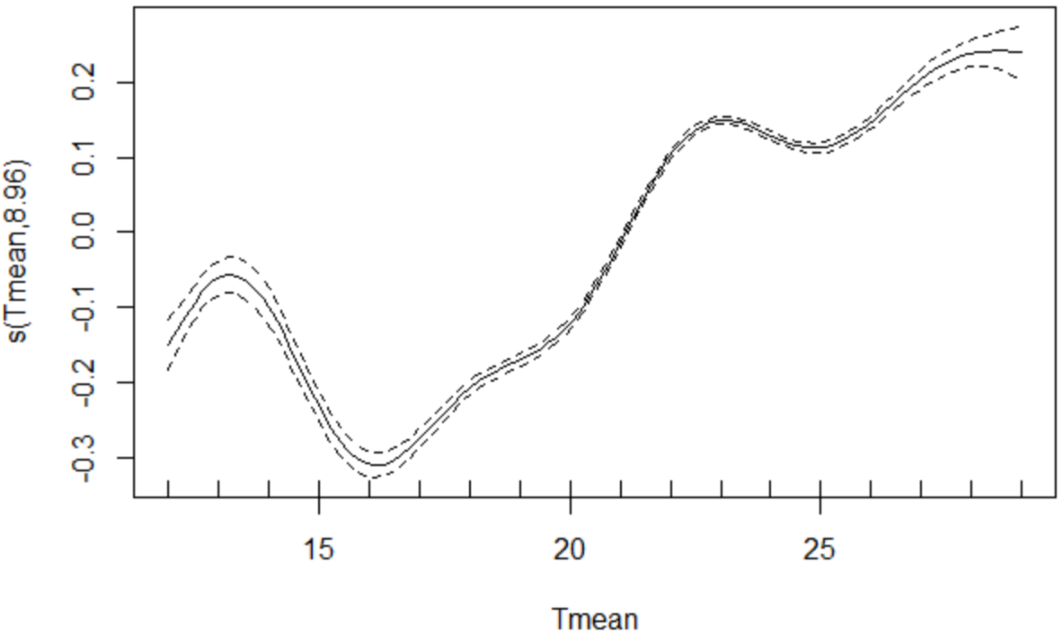

Figure 9.17 – Smoothed weekly mean temperatures (Model VIII)

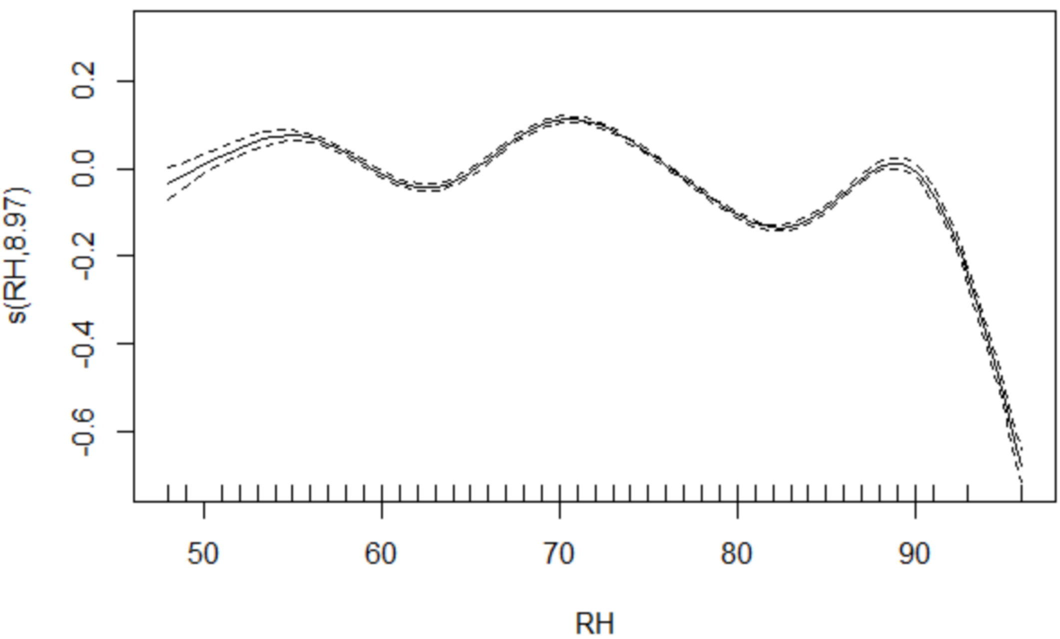

Figure 9.18 – Smoothed weekly relative humidity (Model VIII)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmean) + s(RH)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.332e+00  2.812e-03  2251.6   <2e-16 ***
Mal_1       4.899e-04  1.923e-06   254.7   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(Tmean) 8.964      9  10671  <2e-16 ***
s(RH)    8.972      9   3390  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.722   Deviance explained = 75.4%
UBRE = 81.604  Scale est. = 1         n = 456
```

Figure 9.19 – Summary statistics (Model VIII)

Model IX. Mal = Mal_1 + s(Tmax-15) + s(P-3)

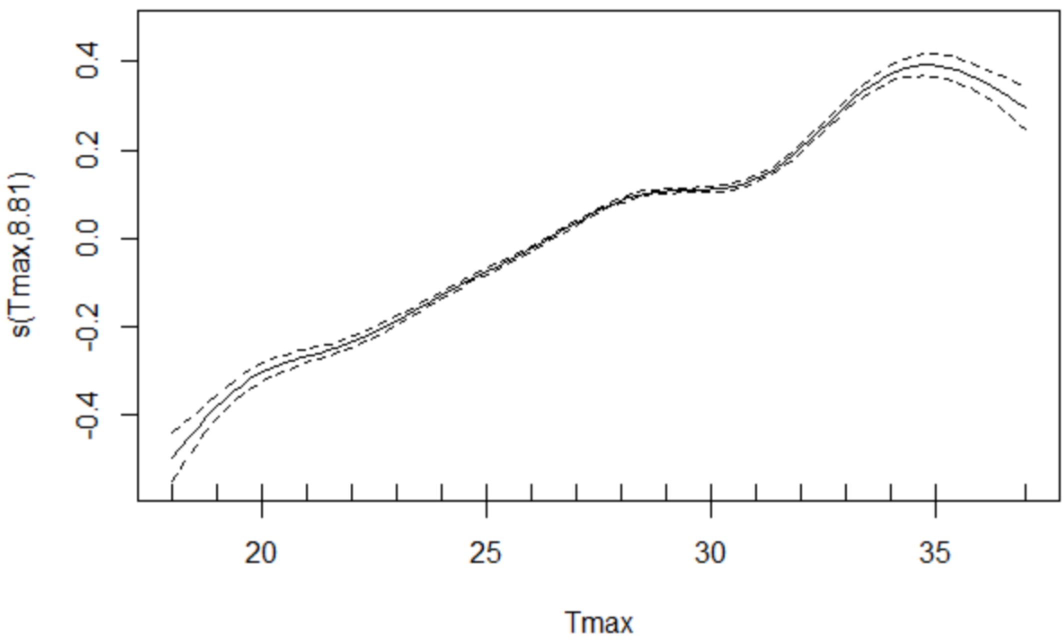

Figure 9.20 – Smoothed weekly maximum temperatures (Model IX)

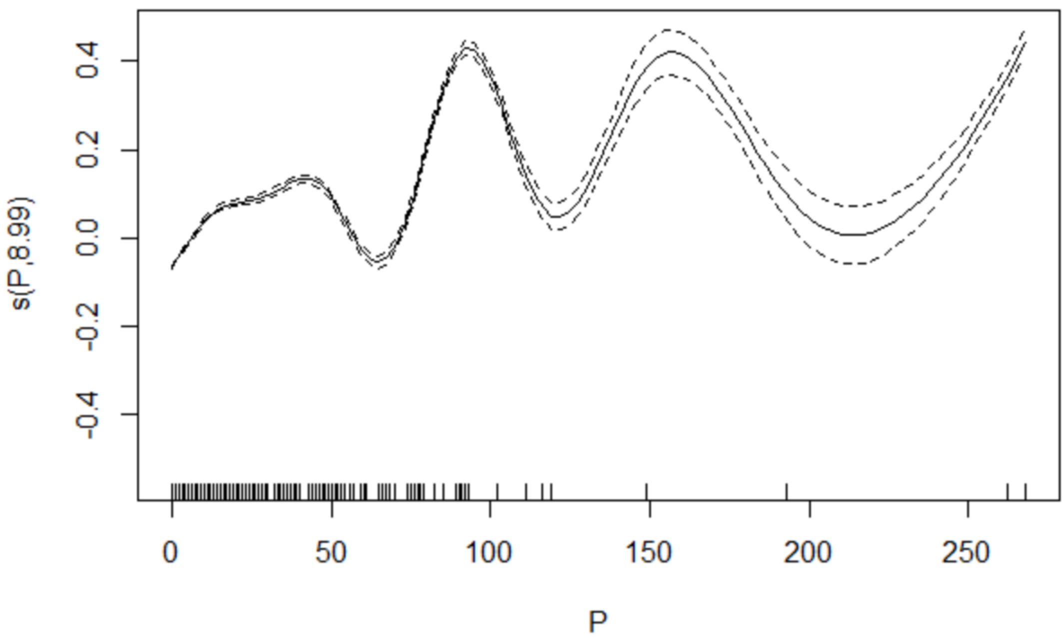

Figure 9.21 – Smoothed weekly precipitation (Model IX)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmax) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.363e+00  3.026e-03  2102.7   <2e-16 ***
Mal_1       4.599e-04  2.185e-06   210.5   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmax) 8.808  8.987   6606  <2e-16 ***
s(P)    8.989  9.000   4934  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.727   Deviance explained = 76.2%
UBRE = 79.488  Scale est. = 1         n = 453
```

Figure 9.22 – Summary statistics (Model IX)

Model X. Mal = Mal_1 + s(Tmin-8) + s(P-3)

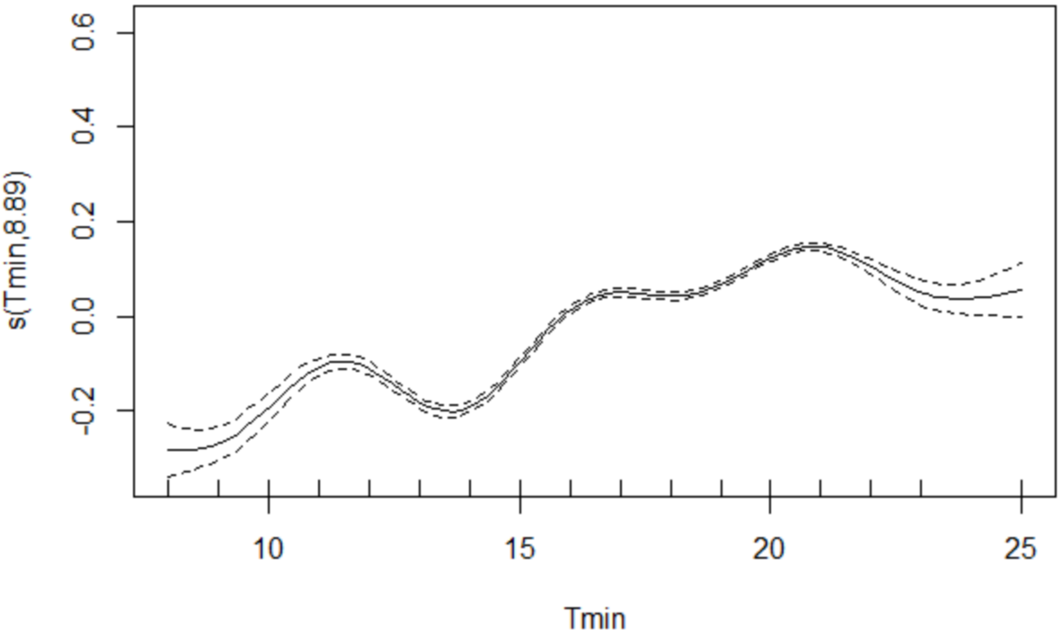

Figure 9.23 – Smoothed weekly minimum temperatures (Model X)

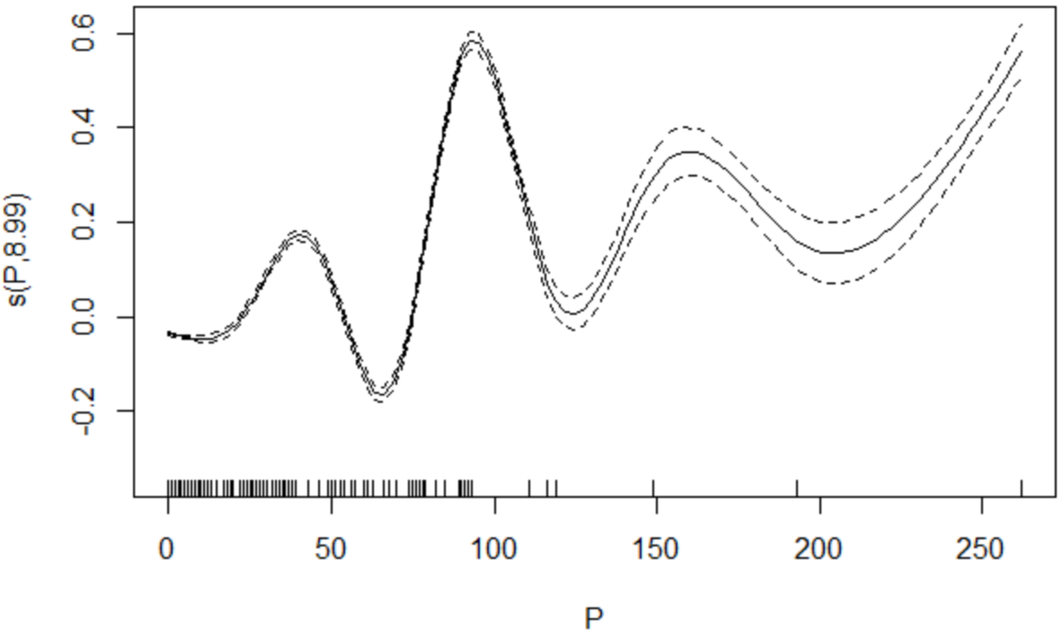

Figure 9.24 – Smoothed weekly precipitation (Model X)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmin) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.239e+00  4.731e-03  1318.5   <2e-16 ***
Mal_1       5.691e-04  4.149e-06   137.2   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmin) 8.887  8.995   2287  <2e-16 ***
s(P)    8.990  9.000   4898  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.691   Deviance explained = 71.6%
UBRE = 62.206  Scale est. = 1         n = 312
```

Figure 9.25 – Summary statistics (Model X)

Model XI. Mal = Mal_1 + s(Tmean-12) + s(P-3)

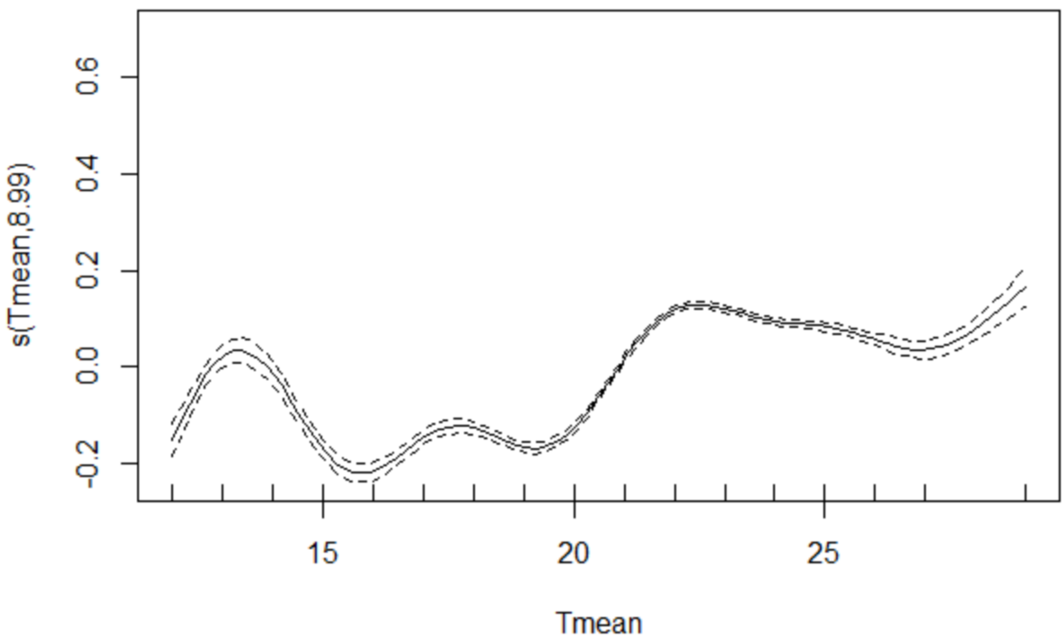

Figure 9.26 – Smoothed weekly mean temperatures (Model XI)

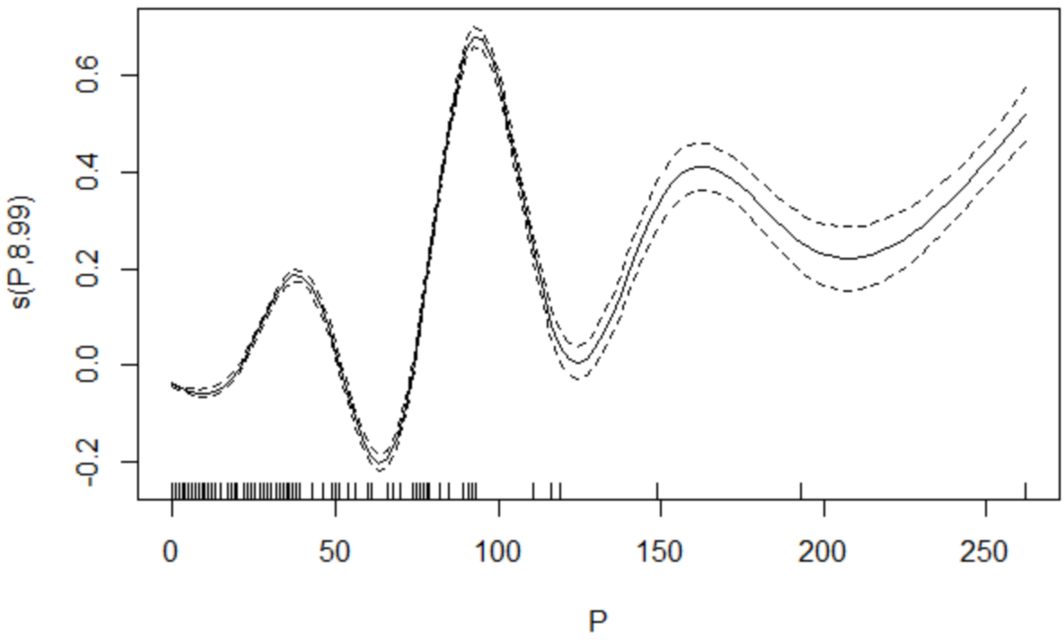

Figure 9.27 – Smoothed weekly precipitation (Model XI)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmean) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.223e+00  4.906e-03    1268   <2e-16 ***
Mal_1       5.742e-04  4.450e-06     129   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(Tmean) 8.985      9   2382  <2e-16 ***
s(P)     8.991      9   6114  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.703   Deviance explained =   72%
UBRE = 58.629  Scale est. = 1         n = 300
```

Figure 9.28 – Summary statistics (Model XI)

Model XII. Mal = Mal_1 + s(RH-2) + s(P-3)

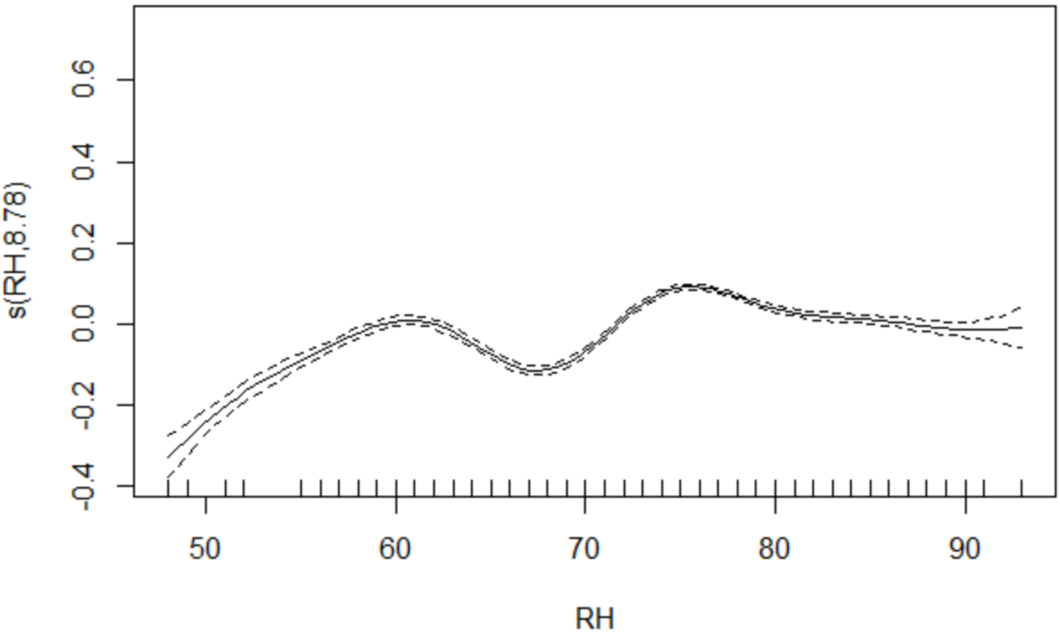

Figure 9.29 – Smoothed weekly relative humidity (Model XII)

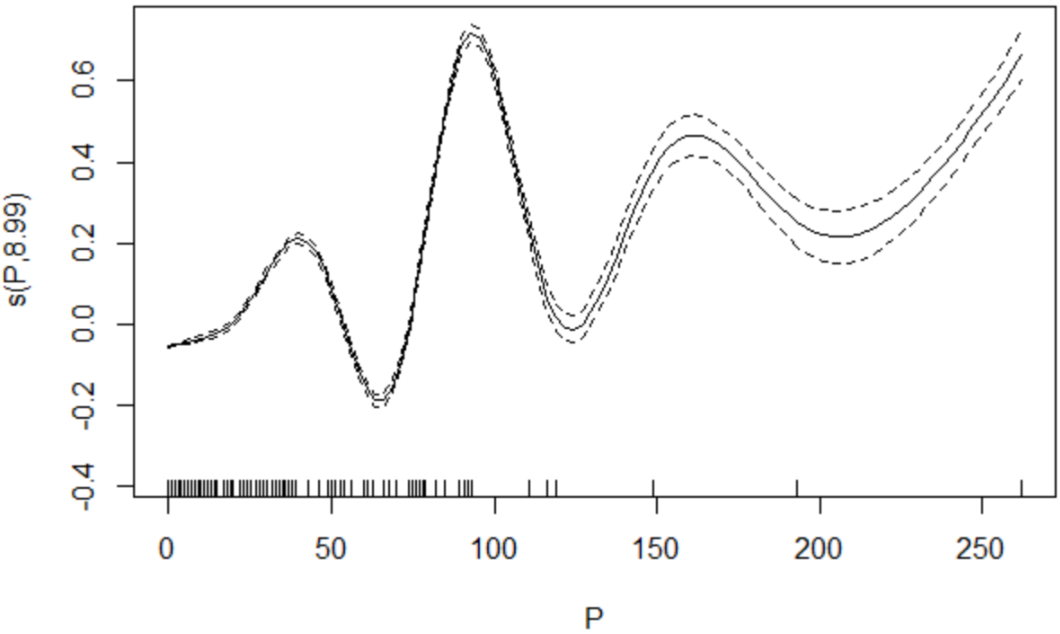

Figure 9.30 – Smoothed weekly precipitation (Model XII)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(RH) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.182e+00  4.745e-03  1302.7   <2e-16 ***
Mal_1       6.315e-04  4.147e-06   152.3   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
        edf Ref.df Chi.sq p-value
s(RH) 8.777  8.984   1067  <2e-16 ***
s(P)  8.991  9.000   6200  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.666   Deviance explained = 68.9%
UBRE = 65.494  Scale est. = 1         n = 311
```

Figure 9.31 – Summary statistics (Model XII)

Model XIII. Mal= Mal_1 + s(Tmax-15) + s(RH-12) + s(P-3)

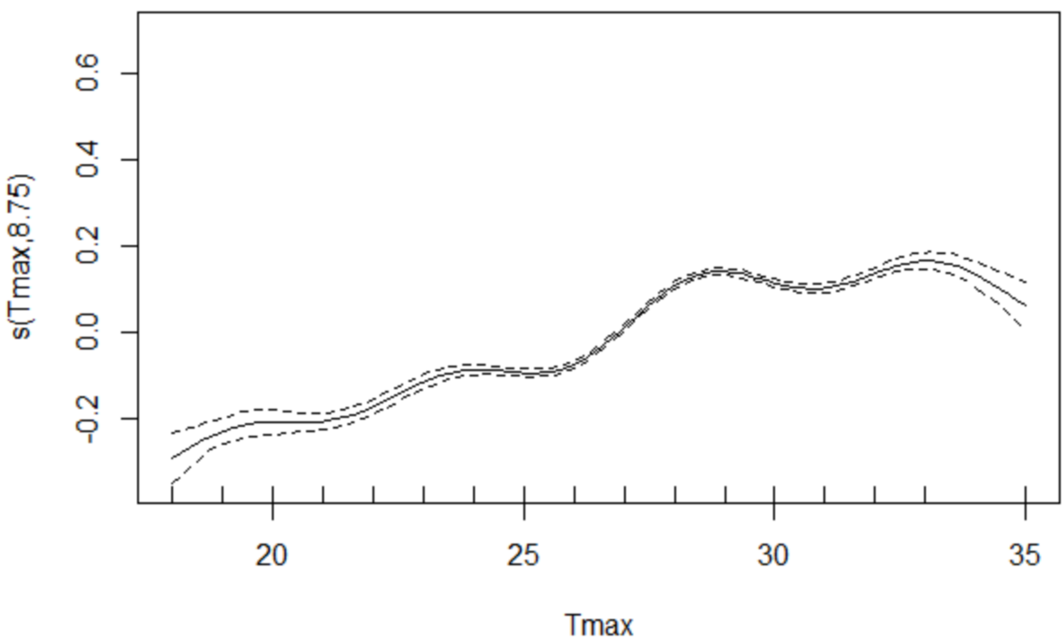

Figure 9.32 – Smoothed weekly maximum temperatures (Model XIII)

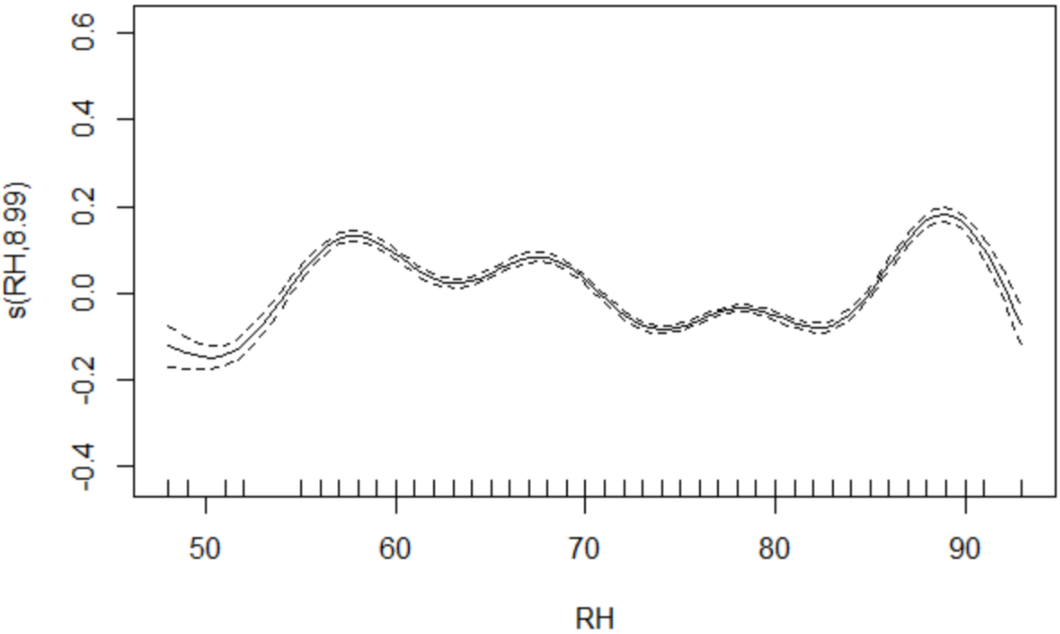

Figure 9.33 – Smoothed weekly relative humidity (Model XIII)

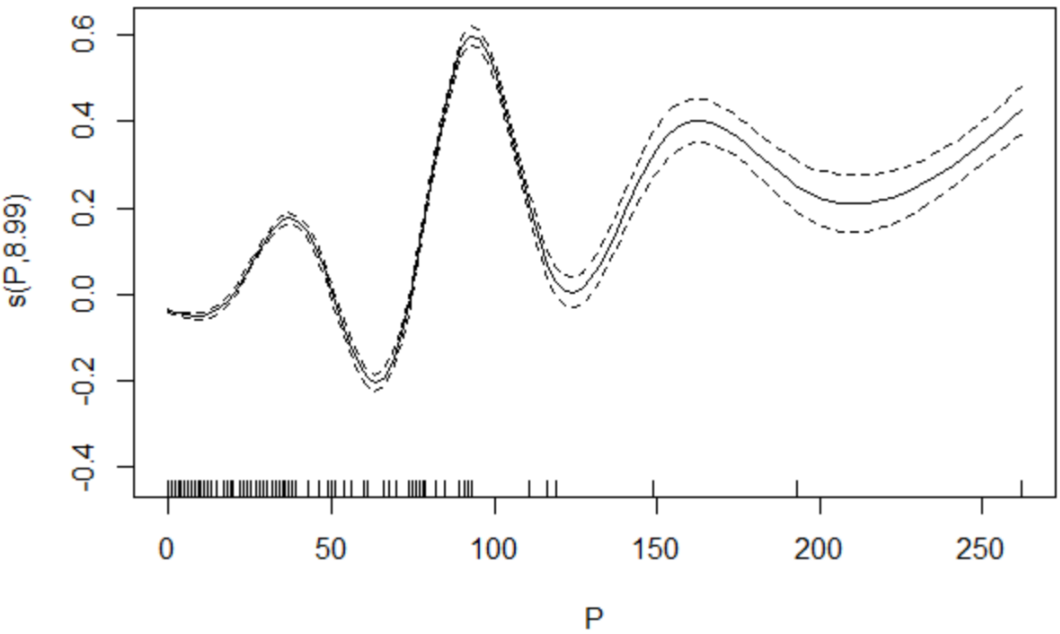

Figure 9.34 – Smoothed weekly precipitation (Model XIII)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmax) + s(RH) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.205e+00  5.007e-03  1239.2   <2e-16 ***
Mal_1       5.881e-04  4.542e-06   129.5   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmax) 8.753  8.977   2442  <2e-16 ***
s(RH)   8.990  9.000   1642  <2e-16 ***
s(P)    8.994  9.000   5510  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.729   Deviance explained = 74.9%
UBRE = 53.123  Scale est. = 1         n = 297
```

Figure 9.35 – Summary statistics (Model XIII)

Model XIV. Mal = Mal_1 + s(Tmin-12) + s(RH-12) + s(P-3)

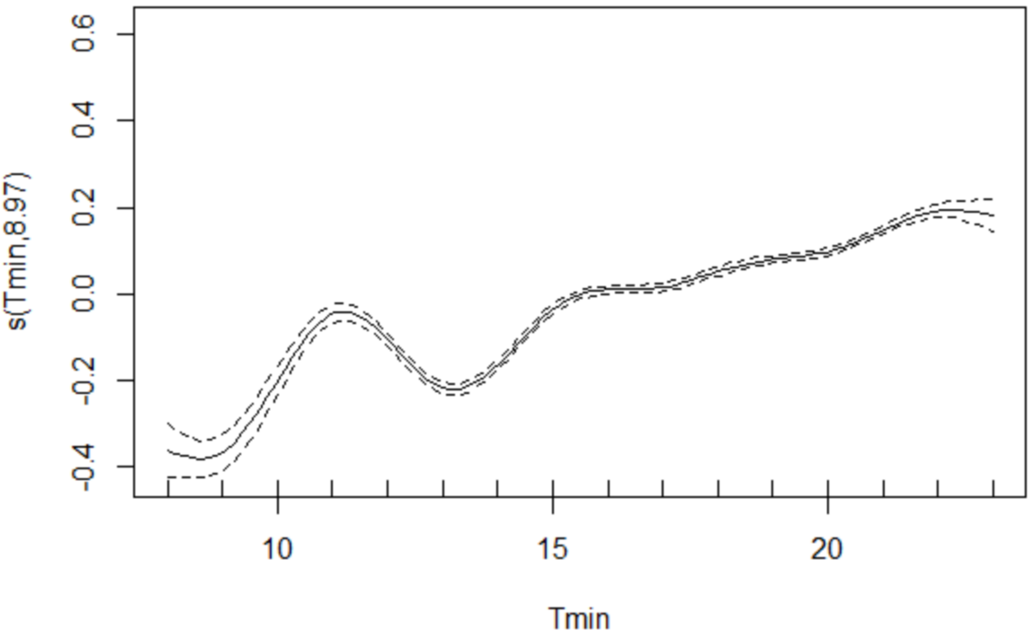

Figure 9.36 – Smoothed weekly minimum temperatures (Model XIV)

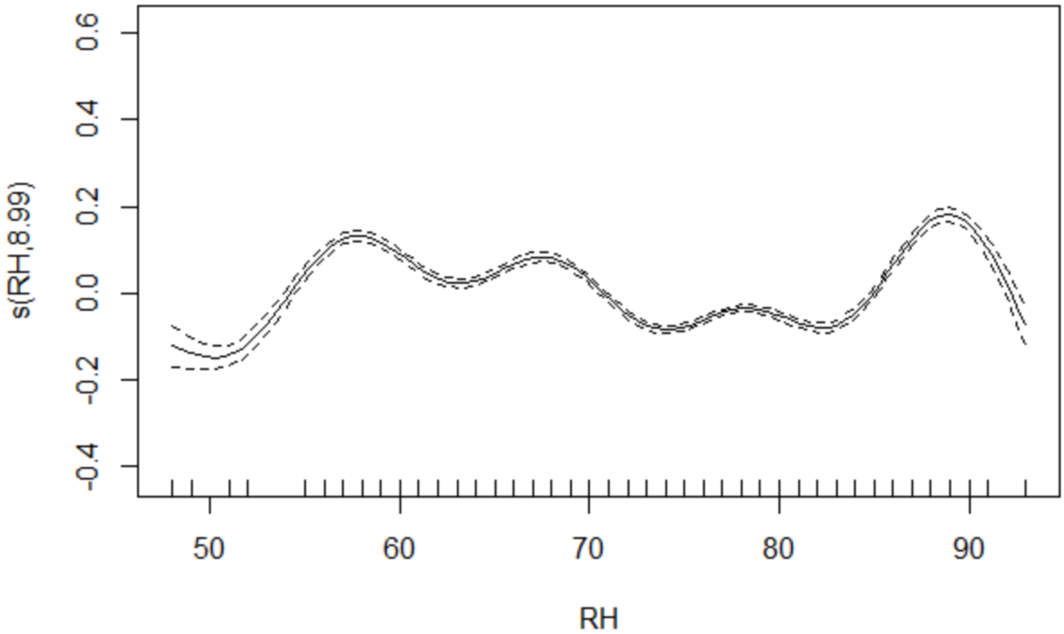

Figure 9.37 – Smoothed weekly relative humidity (Model XIV)

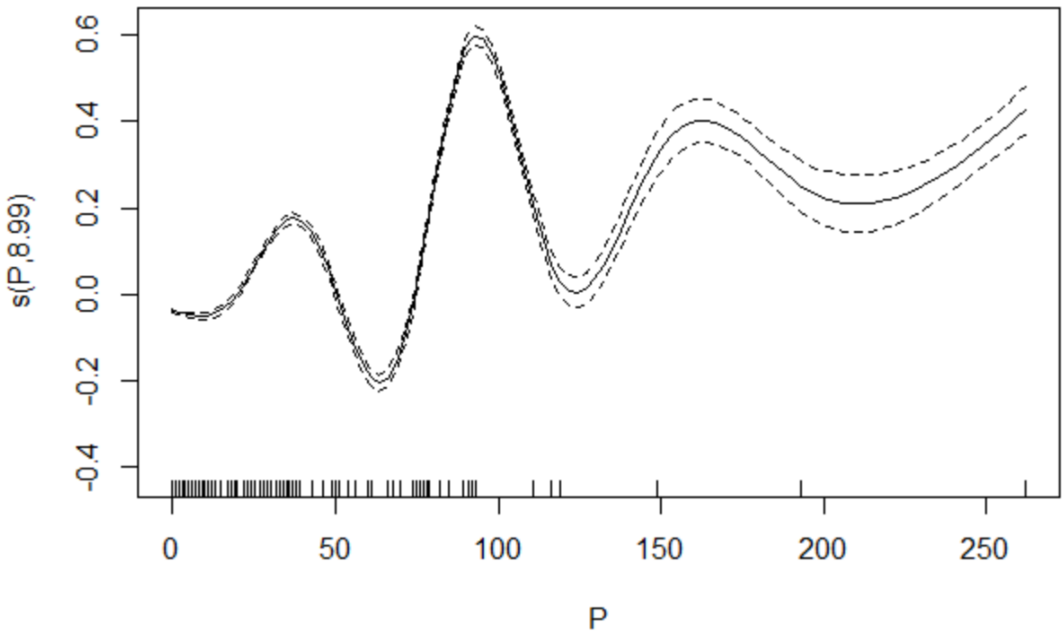

Figure 9.38 – Smoothed weekly precipitation (Model XIV)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmin) + s(RH) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.210e+00  5.086e-03  1221.0   <2e-16 ***
Mal_1       5.844e-04  4.662e-06   125.4   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
          edf Ref.df Chi.sq p-value
s(Tmin) 8.968      9   2018  <2e-16 ***
s(RH)   8.987      9   1360  <2e-16 ***
s(P)    8.990      9   4466  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.717   Deviance explained = 74.1%
UBRE = 54.263  Scale est. = 1         n = 300
```

Figure 9.39 – Summary statistics (Model XIV)

Model XV. Mal = Mal_1 + s(Tmean-12) + s(RH-12) + s(P-3)

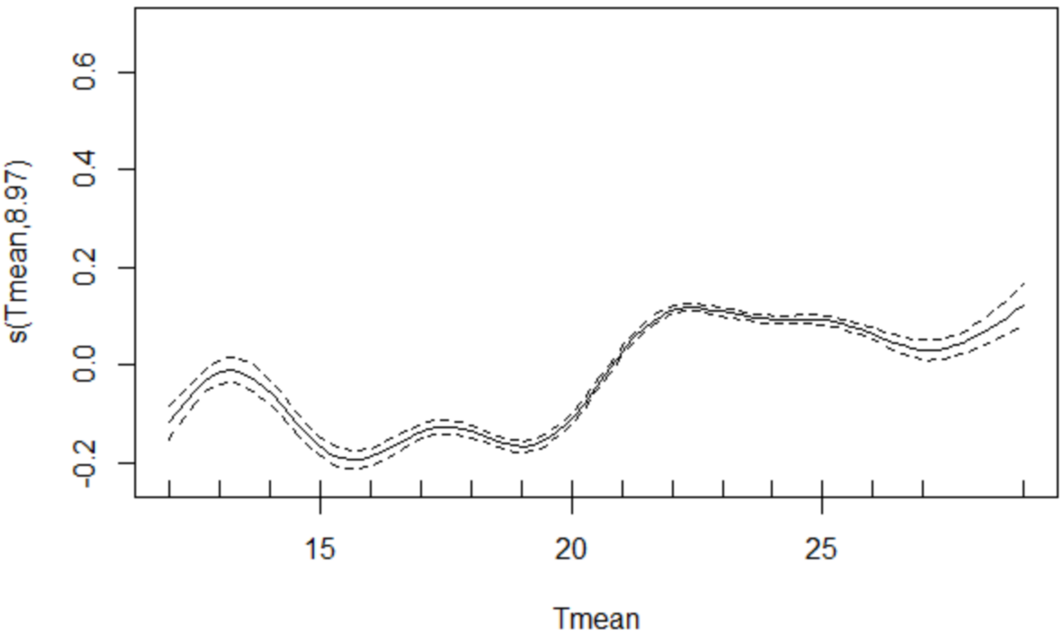

Figure 9.40 – Smoothed weekly mean temperatures (Model XV)

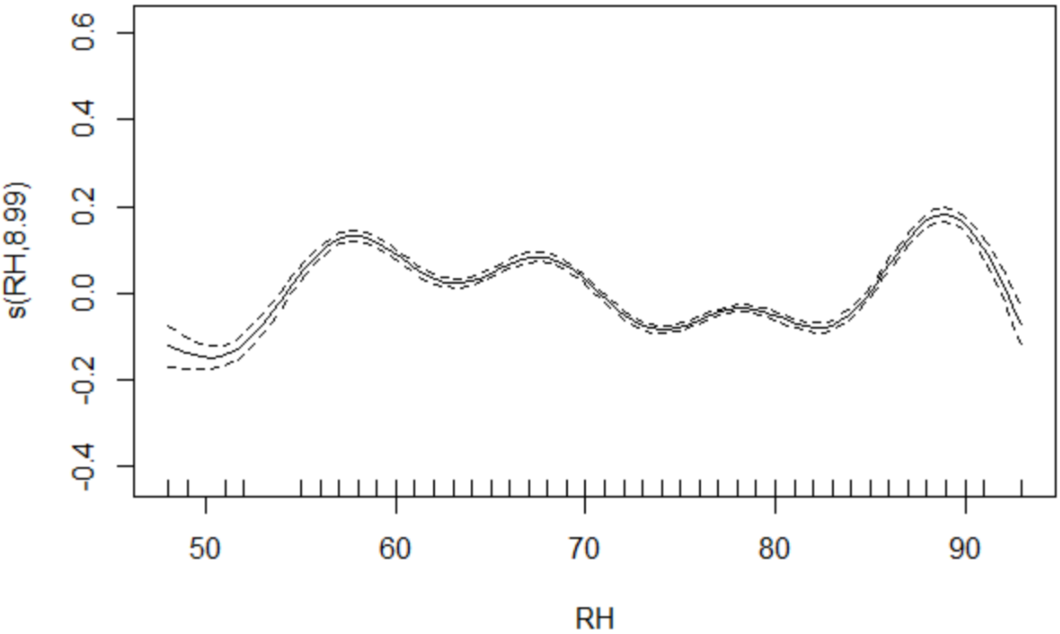

Figure 9.41 – Smoothed weekly relative humidity (Model XV)

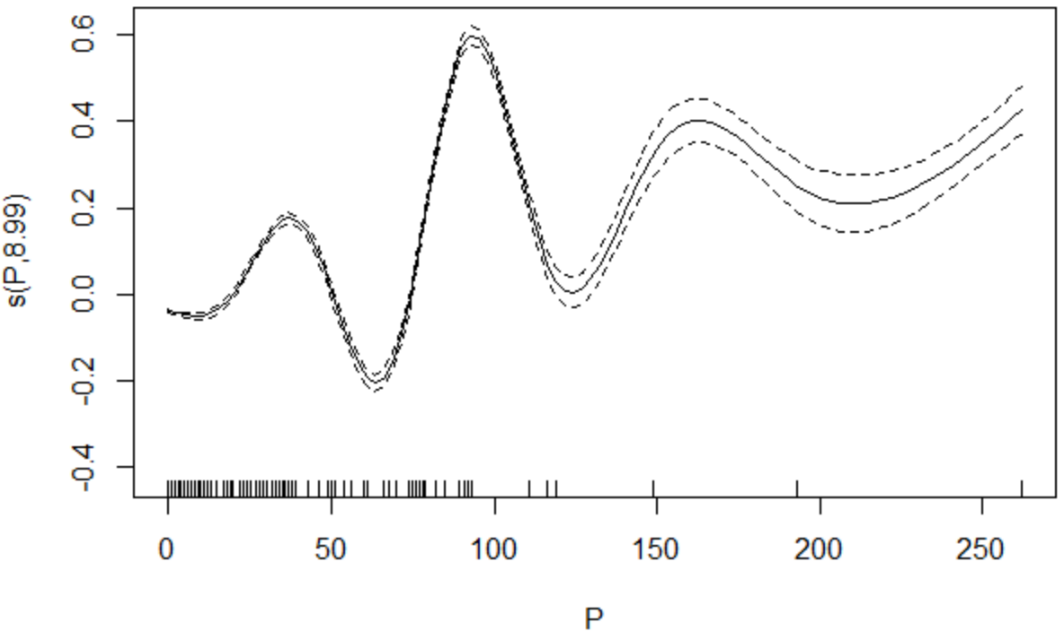

Figure 9.42 – Smoothed weekly precipitation (Model XV)

```
Family: poisson
Link function: log

Formula:
Mal ~ Mal_1 + s(Tmean) + s(RH) + s(P)

Parametric coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 6.209e+00  5.050e-03  1229.5   <2e-16 ***
Mal_1       5.870e-04  4.616e-06   127.2   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(Tmean) 8.969      9   1907  <2e-16 ***
s(RH)    8.982      9   1202  <2e-16 ***
s(P)     8.993      9   5461  <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

R-sq.(adj) =  0.719   Deviance explained = 73.9%
UBRE =  54.71  Scale est. = 1         n = 300
```

Figure 9.43 – Summary statistics (Model XV)